Research evaluation

EVALUATION REPORT OF THE UNIT

LGM - Laboratoire de génétique médicale

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Université de Strasbourg - Unistra
Institut national de la santé et de la recherche médicale - Inserm

EVALUATION CAMPAIGN 2022-2023
GROUP C

Rapport publié le 20/06/2023

High Council for evaluation of research and higher education

In the name of the expert committee[1] :

Juliette Azimzadeh, Chairwoman 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 exact certified data extracted from the deposited files by the supervising body on behalf of the unit.

MEMBERS OF THE EXPERT COMMITTEE

Chairperson:	Ms Juliette Azimzadeh, CNRS, Paris
Experts:	Mr Frederic Checler, CNRS, Valbonne Mr Didier Lacombe, University of Bordeaux (representative of CSS) Ms Anastella Pelet, Institut des maladies génétiques Imagine (representative of supporting personnel) Mr Alain Verloes, Université Paris Cité, Paris 7 (representative of CNU)

HCÉRES REPRESENTATIVE

Ms Marie José Stasia

CHARACTERISATION OF THE UNIT

- Name: Laboratoire de Génétique Médicale
- Acronym: LGM
- Label and number: UMRS_1112
- Composition of the executive team: Ms. Hélène Dollfus

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

UMRS_1112 (Laboratory of Medical Genetics - LGM) is defined as a translational genomic medicine laboratory. Launched in 2003 as an *Equipe d'Accueil* (EA of the University of Strasbourg), then as an Inserm Avenir team (2007), UMRS_1112 is since 2012 an UMR (*Unité Mixte de Recherche)* co-supervised by the University of Strasbourg and Inserm.
The research projects of this single-team unit are divided into two axes and focus on the identification and functional validation of genes involved in rare diseases. Axis 1 is dedicated to the study of rare sensory syndromes, most often with ocular involvement, such as certain retinopathy and ciliopathy (Bardet-Biedl syndrome, Alström syndrome) or certain abnormalities of DNA transcription and repair (Cockayne and related syndromes). Two other themes have recently been added to the organisation chart: 'Genetics of infertility' and 'Chromosomal abnormalities and intellectual deficiency'. In parallel, Axis 2 is dedicated to the therapy of certain ciliopathy with metabolic phenotypes. The leader of Axis 2 created the start-up ALMS Therapeutics, with the objective to extend the findings to more frequent pathologies such as diabetes, obesity or retinal degeneration.
In total, this unit is composed of eight university-hospital physicians (PU-PH and MCU-PH), two consulting hospital physicians (PH), two Inserm full-time researchers (CRCN), three research engineers (of which only one is statutory - Inserm), one assistant engineer on a fixed-term contract, and two technicians (1 statutory HUS, one on a fixed-term contract). Axis 2 is led by an Inserm researcher, Vincent Marion, and Axis 1 is piloted for the whole evaluation period by Hélène Dollfus in general and for ciliopathy, Vincent Laugel for DNA repair anomalies, and at the end of evaluation period Stéphane Viville for infertilities (since June 2021) and Caroline Schluth-Bolard (since sept 2021).

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

Previously located in the research building of the Medical School of Strasbourg (*Faculté de Médecine de Strasbourg*), UMRS_1112 has been relocated to the new CRBS building (*Centre de Recherche Biomédicale de Strasbourg*) on the same campus in 2020. Embedded in the campus of the University Hospitals of Strasbourg (HUS), the unit is close to both the Clinical Genetics Department located on the same building and the medical genetics diagnostic laboratory located in an adjacent building, which favors links with clinical activities.
The CRBS also hosts the CHU three rare disease reference centers and four rare disease competence centres, in the context of which allows for rapid and efficient communication and scientific exchanges with members of the unit.
Furthermore, the CRB'S hosts a total of ten different units (8 UMR and 2 Unistra units), allowing establishing new scientific collaborations (e.g. with the bioinformatics team) and to benefit from efficient technological platforms (preclinical testing facility, microscopy…).

RESEARCH ENVIRONMENT OF THE UNIT

UMRS_1112 is under the aegis of two supervisory bodies: the University of Strasbourg (Unistra) and Inserm.
The unit is the founding research group for the creation of IGMA (*Institut de Génétique Médicale d'Alsace*, a *Groupement d'Intérêt Scientifique* -GIS), which gathers the actors of the site carrying out research on rare genetic diseases. The unit is located on the first floor of the CRBS, just above the hospital department of medical genetics, where the medical genetic consultations take place and which is directed by the Unit director.
Members of the unit are active in three national networks dedicated to rare diseases labelled by the French Ministry of Health (FSMR, Filière de Santé Maladies Rares): i) Sensgene, dedicated to rare sensorial diseases, actually piloted by the Unit Director (UD) for the HUS in Strasbourg ii) AnDDI-RARe, dedicated to genetic developmental anomalies, and iii) DéfiScience, dedicated to genetic intellectual disabilities.
Furthermore, the Unit leader coordinates the European Reference Network Ern-Eye (awarded by the European Commission in 2017) dedicated to rare eye diseases.

UMRS_1112 is one of the founding members in 2016 of the FHU Neurogenycs (*Fédération Hospitalo-Universitaire* NEUROsciences- GENetics-psYchiatriCS). The unit is also a member of the *Institut Thématique Interdisciplinaire (*ITI) Neurostra (IDEX) and a member of the *Fédération de Médecine Translationnelle de Strasbourg* (FMTS). Finally, UMRS_1112 is a member of STRAS&ND (Strasbourg Translational Research on the Autism Spectrum & Neurodevelopmental Disorders), a network composed of research teams and clinical services and more than 60 clinicians and statutory researchers.

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

Permanent personnel in active employment	
Professors and associate professors	6
Lecturer and associate lecturer	4
Senior scientist (Directeur de recherche, DR) and associate	0
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)	5
Subtotal permanent personnel in active employment	17
Non-permanent teacher researchers, researchers and associates	1
Non-permanent research supporting personnel (PAR)	2
Post-docs	0
PhD Students	1
Subtotal non-permanent personnel	4
Total	21

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

Employer	**EC**	**C**	**PAR**
Université de Strasbourg	10	0	0
Inserm	0	2	3
CHU Strasbourg	0	0	2
Total	10	2	5

UNIT BUDGET

Recurrent budget excluding wage bill allocated by parent institutions (total over 6 years)	505.0
Own resources obtained from regional calls for projects (total over 6 years of sums obtained from AAP idex, i-site, CPER, territorial authorities, etc.)	900.0
Own resources obtained from national calls for projects (total over 6 years of sums obtained on AAP ONR, PIA, ANR, FRM, INCa, etc.)	1825.0
Own resources obtained from international call for projects (total over 6 years of sums obtained)	770.0
Own resources issued from the valorisation, transfer and industrial collaboration (total over 6 years of sums obtained through contracts, patents, service activities, services, etc.)	940.0
Total in euros (in k €)	4940.0

GLOBAL ASSESSMENT

The Laboratoire de Génétique Médicale (LGM) is a Medical Genetics Laboratory dedicated to translational research in the field of rare diseases such as ciliopathy & related syndromes, DNA repair/transcription diseases with Cockayne & related syndromes and other ultra-rare syndromes (the genetic of infertility). In 2012, this unit has become a mixed University de Strasbourg (Unistra) – Inserm Unit namely UMRS_1112. Two axes are developed. Axis 1 encompasses a wide field of research in medical genetics ranging from analysis of clinical and phenotypic data to novel gene identification, and axis 2 is dedicated to the search for therapeutic options to treat ciliopathy which has led to the creation of a spin-off company, ALMS Therapeutics. The unit relocated in 2020 to the CRBS (Centre de Recherche Biomédicale de Strasbourg) in the campus of the Strasbourg medical school, which represents a great opportunity for its future development. The proximity with the HUS medical genetics department, and with three reference centres for rare diseases which are also led by members of the unit, allows a remarkable integration of research and clinical activity. This aspect is reinforced by the creation of the IGMA (*Institut de Génétique Médicale d'Alsace*), in which the members of the unit have played a determining role. This places the unit in direct interaction not only with its partners for clinical research, but also with nine other units dedicated to biomedical research, with which the unit shares technological platforms and administrative support.
The unit has shown an excellent capacity to mobilise financial resources, the recurrent funding given by the host institutions, not including salaries, representing only 10% of its budget. The rest of the funding comes mainly from national calls (37%, ANR, FRM, INCa), as well as from regional (18%, AAP Idex, i-Site, CPER, territorial authorities), international calls (16%, H2020 – Maria Sklodowska-Curie Action innovative training network, European joint program on rare diseases, ANR DFG), and industrial partnerships (19%, Inflectis firm). The scientific strategy of the unit is excellent. UMRS_1112 has been a driving force in the construction of its current environment, with the installation in the vicinity of medical diagnostic infrastructure and national and European rare disease networks (Rare eye disease networks: France & Sensgene - Europe & Ern-Eye) which it helps to coordinate. This synergy between fundamental research, translational research and clinical activity is a great achievement. Despite this remarkable improvement in working conditions brought about by the relocation, the unit still suffers from a drastic lack of personnel, especially technical personnel, which places it in a vulnerable position for the pursuit of its research objectives. The second axis devoted to translational research, although very successful, could not be reinforced and remained carried by a single researcher (CRCN, Inserm), who will leave the unit during the next term. In addition, the committee is not convinced by the addition of a new research topic devoted to the genetic of infertility, which is thematically more distant from the other issues addressed, in a context where it is preferable to concentrate human resources on a smaller number of projects. The functioning of the unit is good to very good. The follow-up of the careers of the technical staff is satisfactory, but their limited number makes the working conditions difficult and has a negative impact on personal relations. A framework exists for the scientific animation and the follow-up of projects (weekly scientific and organisational meetings, monthly meetings for, among other things, the scientific strategy). In addition, the human resources are highly represented by MCU-PH and PU-PH (so-called 'hospital university' positions) who carry both hospital and university activities therefore with seldom time for mentoring PhDs students. Thus, the numerous responsibilities of the researchers of the unit in the clinic, in teaching, or in the animation of scientific networks, which weigh particularly on the PI's availability, reduce the time devoted to the organisation of the scientific life of the unit and harms its functioning.

The recognition and attractiveness of UMRS_1112 are excellent and illustrated by numerous contributions to European and international events (Ontology for Rare Eye Diseases – Mont Saint-Odile Ern-Eye international workshop Genetic & molecular diagnoses for Rare Eye Diseases 2018, Florence international Ern-Eye workshop 2019 …–, successes in European calls for proposals – H2020 – Maria Sklodowska-Curie Action innovative training network, European joint program on rare diseases, ANR DFG – and national and European rare disease networks – national network FSMR Sensgene and the European reference network Ern-Eye – which it helps. In addition, the unit has been awarded funding by the PIA programs as co-leads or PI. These include a LABEX project – GENMED – and a RHU project – CIL-ICO –. They have also been successful in responding to the call 'Rare diseases: solving diagnostic deadlocks' from the PIA and ITMO GGB – Génétique, Génomique et Bioinformatique – and the PIA – Inserm Cohortes framework. The unit has also shown a remarkable dynamism to reinforce its staff by attracting researchers through mobility. Two associate professors-hospital practitioners – MCU-PH –, two professor-hospital practitioners – PU-PH – and one full-time researcher – CRCN Inserm –, have joined the unit in the last few years 2018–2021) to develop two new topics. This tendency should be maintained in the short term with the planned arrival of new members to reinforce the topic of intellectual deficiencies related to chromosomal anomalies. However, departures one MCU and one technician for different reasons have occurred in parallel, and human resources remain fragile with respect to researchers, although less dramatic than for technical staff.

The scientific production of UMRS_1112 is excellent, with a constant production during the evaluation period including 63 peer reviewed scientific articles of which 25 where UMRS-1112 has a leading position (first and/or last authors are from the laboratory) and some in leading journals (Nature Comm, Embo Molecular Medicine, Human Mutation, Bioinformatics…). Eleven additional publications are position papers, which shows the level of seniority of certain members of the laboratory for matters such as genomics applied to rare diseases or rare disease research. All the PhD students and Postdoctoral fellows have published at least one article in good quality journal at a leading position. The major asset of the unit is to have built up cohorts of patients, thanks in particular to the rare disease reference centres linked to the unit (especially the Centre for rare eye diseases Cargo with the FSMR SENSGENE, the CRMR for genetic developmental anomalies with the FSMR AnDDI-RARe, the CRMR for genetic intellectual disabilities with the FSMR DéfiScience), as well as the lead of the UD in the national network FSMR Sensgene and the European reference network Ern-Eye. However, there is a disproportion between the two axes from the point of view of publications, which are mostly generated by Axis.
1. However, this can be explained in part by the number of people involved in Axis 1 and the fact that Axis 2 is more dedicated to translational research.

Interactions with the non-academic world are excellent, as illustrated by the development of a spin-off company (ALMS Therapeutics) which is due to enter clinical phase in 2023 in the US. Four maturation grants from Satt Conectus, four contracts with industry, and seven European and US patents have been obtained by the PI of the axis 2. During 2016 -2021, Interactions with the public are numerous and include radio and television interviews (32 outreach activities by the DU and a PI has also performed 7 outreach activities for identical lay audiences). The PI also organised meetings with patient associations (Annual gala of the patient's firm event with presentation to public, funding events of patient's groups such as Formicoeur, Rare Disease day…). In addition, the unit is strongly involved in patient care support by writing numerous guidelines and recommendations for medical institutions and rare disease network organisations (national network FSMR Sensgene and the European reference network Ern-Eye).

DETAILED EVALUATION OF THE UNIT

A - CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The recommendations of the previous committee are in bold text.

1. Considering the scope of the projects currently carried out by this relatively small team, it is recommended to refocus the forces on the most promising physiopathological and therapeutic projects.
During the period evaluated, the team remained mainly dedicated to its long-standing research interests, which are, on the one hand, the identification and phenotype-genotype correlations for rare diseases, retinopathy, ciliopathy and DNA repair/transcription diseases (Axis 1), and, on the other hand, the development of models and therapeutic approaches for ciliopathy and their application to more common diseases such as diabetes. In addition, human resources have been reinforced by the arrival of one full-time researcher (CR Inserm), two assistant professors and hospital practitioners (MCU-PH), and two professors and hospital practitioners (PU-PH). Another assistant professor (MCU) was hired in 2019 but had to resign in 2020 due to a medical condition. This led to reinforcement of the team on DNA repair/transcription diseases, and the team on ultra-rare diseases, retinopathy and ciliopathy (Axis 1). Two other researchers bring new research topics, centred on the genetics of infertility and intellectual disabilities related to chromosomal abnormalities, respectively.

4. The expert committee recommends attracting at least one full-time researcher (in addition to the postdoctoral fellow programmed for one of the projects of axis 2 on retinopathy). With the diversification and increasing volume of the nature of the data to be analysed, it is important to ensure that the analysts are well trained and that adequate computer resources are available.
One researcher joined in the course of the previous mandate to work on DNA repair/transcription diseases. The hiring of bioinformaticians has not been possible due to a lack of permanent positions available within supervising bodies. Overall, human resources remain hugely concerning for the unit, most acutely with respect to technical staff.

5. The expert committee recommends that the setting up of internal seminars and the participation of students in seminars outside the unit be encouraged. Concerning teaching through research, given the quality of the results already obtained by the team and its scientific potential, it is essential that the person in charge of the second thematic axis passes his HDR.
Internal seminars where students can present their work are held weekly, and students are encouraged to present their work at conferences. The relocation to CRBS now also allows students to interact with members of other units housed within the building. For instance, the students had the opportunity to present their work during a common event named 'CRBS days'.
The researcher in charge of Axis 2 has not yet passed his HDR but two other researchers have done so during the period under consideration, and two of the researchers who have joined the unit have an HDR.

6. At this stage of the unit's development, given the diversity and ambition of the projects in progress, it is necessary to focus efforts on a smaller number of projects by trying to prioritise the functional/physiopathological studies as much as possible. As it was clarified during the discussion of the committee members with the director, a prioritisation of the physiopathological projects is indeed planned with: 1/the continuation of the therapeutic project in the field of obesity and diabetes
The therapeutic project in the field of obesity and diabetes has been pursued and has resulted in 2 publications, 5 patents and the creation of a start-up during the period under review.

2/ the recruitment of a postdoc on the project related to retinopathy (ITN Marie Curie);
A PhD student was recruited to work on a translational project for the treatment of retinopathy axis 1 & 2 – on the H2020-MSCA-ITN-2016 Maria Sklodowska-Curie call the UD being the local PI – PhD thesis 'Electromagnetic Nanoparticles as vectors of pharmacological treatment for retinal degeneration' – .

3/ the finalisation of the work in progress on the renal damage in BBS, without continuing beyond that.
This line of work has not been pursued as advised by the previous committee.

B - EVALUATION AREAS

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

Assessment on the unit's resources

The resources of the unit are excellent. The unit mobilises about 90% of its budget, salaries not included, by its own means, with most of it coming from national calls (37%). The unit functions in excellent adequacy with its immediate environment, particularly since its installation within the CRBS, which places it in direct interaction with clinical research. A point of great concern, however, is that of human resources. In particular, the unit suffers from a critical lack of technical staff, with worrying prospects for next term.

Assessment on the scientific objectives of the unit

The scientific strategy of the unit, which focuses on a range of rare and ultra-rare genetic pathologies, is excellent. The unit benefits particularly well from its immediate environment, in direct interaction with the medical diagnostic infrastructure, from the national and European rare disease networks that it contributes to coordinating, and from the clinical expertise of its members. This total interweaving of basic research, translational research and clinical activity is an inspiring model. The development of axis 2 devoted to translational research has nevertheless been constrained by the fact that only one researcher was involved during the previous mandate.

Assessment on the functioning of the unit

The functioning of the unit is good to very good. Career development is quite satisfactory, but the heavy workload and the small number of staff, especially in terms of technical personnel, make working conditions difficult and have a negative impact on personal relationships. An additional effort must be made in terms of work organisation, in particular as regards the definition of the role of researchers in the supervision of the work of technical staff and students, and communication related to the functioning of the unit in general.

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

Strengths and possibilities linked to the context

The unit's activity is in excellent agreement with its assignments. It is split between academic activities, which represent the major part of the activity, and translational research. The head of the unit, one full-time researcher and 8 professors or assistant professors and hospital practitioners are involved in basic research, while a second full-time researcher is devoted to translational research and the management of a start-up. Permanent technicians or engineers (4 people during the evaluation period, 1 currently) are entirely dedicated to research activities. The director also dedicates an important part of her activity to expertise and participates to the elaboration of national or European plans for the care and research on rare diseases (*Plan France Médecine Génomique* Inserm, *Plan national maladies rares*, European reference network - Eye diseases and ERN coordinators group).
The majority of the unit's researchers are also hospital practitioners, and an important part of their activity is therefore devoted to clinical work as well as managing networks dedicated to rare diseases. Hélène Dollfus is the coordinator of the FSMR-Sensgene network and of the European network Ern-Eye. Members of the unit are responsible for HUS reference centres for rare eye diseases, genetic developmental anomalies and genetic intellectual disabilities.
The unit has shown an excellent capacity to mobilise financial resources, the recurrent funding given by the host institutions representing only 10% of its budget. The rest of the funding comes mainly (37%) from national calls, as well as from regional (18%) and international (16%) calls, and industrial partnerships (19%).

The sharing of resources and support for innovative research themes are very good. Recurrent credits are shared within the unit, and equipment and reagents are mutualised between the different projects in order to rationalise their use. Credits are also made available to young researchers to enable them to start their research projects. The adequacy between the research activity of the unit and its immediate environment is excellent, largely due to the recent relocation to the CRBS. The unit has shared offices with the clinical department, which facilitates interactions between scientists and clinicians. An imaging platform is also available in the CRBS building. The staff of the FSMR-Sensgene and Ern-Eye networks will also soon move to the CRBS, which will further strengthen interactions with the research activity.

Weaknesses and risks linked to the context

The question of human resources is of great concern for this unit, particularly from the point of view of technical staff. Three permanent engineers or technicians have been involved during the mandate, one of whom has retired in 2021 (position replaced in 2022), and the other (the only bioinformatics engineer in the team) has left on mobility- a replacement has been asked for.
The number of full-time researchers is also low (2/12). The other researchers all have clinical tasks in addition to their research activity, and eight of them also have a significant teaching load. The time devoted to research activities and to the supervision of young researchers is therefore limited under these conditions.
Moreover, if the installation of the unit in its new premises is globally an excellent opportunity, it has caused delays in recent years and continues to do so, in particular, concerning the organisation of preclinical testing.

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

Strengths and possibilities linked to the context

The scientific strategy of the unit is clearly established. It is focused on rare genetic diseases, in particular retinopathy, ciliopathy and DNA repair/transcription diseases, and is divided into two axes. Axis 1 concerns the identification of new genes and phenotype-genotype correlations, and Axis 2 the development of therapeutic approaches.
This strategy is in line with the environment and the missions entrusted to the unit by the supervising bodies. The unit shares premises with the HUS medical genetics department, which is also directed by Hélène Dollfus. Unit members are involved in the diagnosis of patients with rare diseases and the identification of associated mutations, as well as in medical counselling.
The unit also has many interactions with other research centres in Strasbourg. The unit collaborates with teams from the IGBMC (*Institut de génétique, biologie moléculaire et cellulaire*) and uses the platforms of the IGBMC and the ICS (*Institut clinique de la souris*) on the nearby Illkirch campus. The unit is a member of regional networks bringing together researchers and clinicians, FHU Neurogenycs and STRAS&ND.
The scientific strategy is discussed in monthly meetings with the senior researchers of the unit. All the members of the unit participate in two weekly meetings, one dealing with organisational issues, and the second with scientific issues related to the development of research projects, or dedicated to literature survey. The laboratory council, composed of all the members of the unit and of student representatives, meets once or twice a year.

Weaknesses and risks linked to the context

If the arrival of new researchers is an asset for the unit, it has nevertheless led to a broadening of the scope of research topics within Axis 1. These new projects might rely on common methodological approaches, but they are not necessarily similar in terms of underlying mechanisms. In particular, the project related to the genetics of infertility is the most divergent, and is led by a single researcher, which risks dispersing the already limited personnel of the unit.
On the other hand, the second axis, which occupies an important place in the scientific strategy of the unit, has not been further developed during the past mandate. This axis is led by a single researcher, who is also very involved in the creation of the start-up ALMS-Therapeutics of which he is the president. Far from being strengthened, this axis will probably disappear during the next mandate because of the announced departure of this investigator from the unit.

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 unit implements the recommendations of the supervising bodies in terms of gender equality and the prevention of other discrimination. The PI was also involved in various events aimed at drawing attention to career inequalities between men and women.
Staff have access to training programs offered by Inserm and the University of Strasbourg and are encouraged within the unit to take advantage of these training opportunities.
The unit assists in the preparation of applications for career advancement, with success since one promotion was obtained during the mandate (from IE to IR).
Risk prevention is applied in compliance with the guidelines issued by the supervising bodies.
IT security practices are adequate and comply with the directives given by the supervising bodies. Data are stored locally within the CRBS or via the Cloud system provided by Unistra (Seafile). Genomic data are stored on a Linux cluster. Experimental data are stored via an electronic laboratory notebook system (Labguru).
The business continuation plan, involving the use of remote work and video conferencing was successfully implemented and tested during the pandemic.

Weaknesses and risks linked to the context

Some staff members mentioned weaknesses in the management of their activity, which seem to be related to a work organisation problem. The PI has many responsibilities outside the unit (coordinator of the Ern-Eye, of the FSMR Sensgene, head of the HUS department of medical genetics…) and probably cannot be as present, regarding the research projects, as she would like. This impacts the work of technical staff which do not systematically have designated co-supervisors. The researchers themselves suffer from this lack of availability, which makes it more difficult for them to take charge of the work organisation.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The recognition and attractiveness of UMRS_1112 are excellent and illustrated by numerous contributions to European/international events, successful applications to European calls, their participation to various international societies, as well as their ability to reinforce the staff by recruiting several professors and assistant professors (PU-PH and MCU-PH) and one full-time researcher (CRCN Inserm), who has moved from the IGBMC.

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 international recognition and attractiveness of UMRS_1112 are excellent and illustrated by numerous (34 in total) invitations to give lectures at European and international meetings. Further, the unit director has been involved in the organisation of four international workshops in the field of rare diseases. She and other members of UMRS_1112 have been either president or members of French and European scientific committees (ERC, FRM, Retina France, AFM-Téléthon, among others). Members of the unit belong to several editorial boards (Ophthalmic Genetics – Elsevier – and Ophthalmic Research – Karger) and are frequently solicited to review articles in international journals. They provide expertise in various scientific committees and boards of clinical trials (Novartis, Janssens – MeiraGTX, Pfizer, Roche…). They are members of multiple learned societies (ASHG, ESHG, ISGEDR, Arvo, the World muscle society, the European Paediatric Neurology Society). Noteworthy, the PI is a senior member of the Institut Universitaire de France. She was also awarded national and international prizes (Christian Hamel prize – Société de Génétique Ophtalmologique Francophone, Médaille d'argent du mérite Typhophille de la Fédération des aveugles de France).

Weaknesses and risks linked to the context

No real weaknesses have been identified.

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

Strengths and possibilities linked to the context

The unit offers excellent working conditions for early career researchers. PhD students and postdocs are supervised by a senior staff member and assisted by technical staff. Students are trained throughout their courses in the program of the doctoral school of the University of Strasbourg, and through participation in national and international conferences. Students have the opportunity to present their data orally during the weekly meetings of the unit, as well as to take part in journal clubs.
In the last few years, the unit has also welcomed several young and senior researchers who have integrated the ongoing projects and thus strengthened the research themes. This includes one full-time researcher CR Inserm, who moved from the IGBMC, two assistant professors and hospital practitioners (MCU-PH), and two professors and hospital practitioners (PU-PH).

Weaknesses and risks linked to the context

The unit did not host renowned international guest researchers

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 outcome of the unit in national and international funding applications is really impressive. The unit has obtained funding from European agencies in which members of the unit are all PI (H2020 – Maria Sklodowska-Curie Action innovative training network, European joint program on rare diseases, ANR DFG). In addition, the unit has been awarded funding by the PIA programs as co-leads or PI. These include a LABEX project (Genmed) and a RHU project (CIL-ICO). They have also been successful in responding to the call 'Rare diseases: solving diagnostic deadlocks' from the PIA and ITMO GGB (*Génétique, Génomique et Bioinformatique*). Finally, the Unit director leads a project within the PIA-Inserm Cohortes framework.

Weaknesses and risks linked to the context

The unit does not lead ANR projects.

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

Strengths and possibilities linked to the context

Overall, the equipment of the unit is excellent and allows cutting-edge investigations. Rodent retinal investigations are possible thanks to newly acquired equipment including a Celeris rodent testing system for performing electroretinograms, an optical coherence tomograph and a Y-maze behavioural setting. The unit also takes advantage of numerous local and national platforms, including the sequencing and imaging platforms of the IGBMC. The unit has devoted space to perform histology, microscopy, acid nucleic purification and bacteriology.
The unit aims at developing iPSCs technology and organoids and has acquired the adequate setting.

Weaknesses and risks linked to the context

The unit is very dependent on external platforms, including platforms outside of the CRBS. This can lead to limitations of access, although this does not apparently hinder the research of the unit.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The scientific production of the unit is excellent. UMRS_1112 had a consistent scientific production from 2016 to 2021, including 96 papers, i.e. more than during the precedent period (92). There is a disproportion between the two axes regarding publications (mainly Axis 1) and patenting (mainly Axis 2). The strengths of the unit come from the patient cohorts, the recruitment via the three rare diseases reference centres (CRMR) linked to the unit, and the involvement of the unit director in the national network FSMR Sensgene and the European Reference Network ERN-EYE, both led by her.

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

Strengths and possibilities linked to the context

The laboratory is only one team with two major axes. This structure is expected to evolve in 2022 to a more complex structure through the adjunction of new groups. Some changes in the composition of the unit occurred only recently (such as the addition of new themes on intellectual deficiency and infertility linked to the arrival of new professors from mid 2021), and the evaluation therefore only takes into account the unit members who contributed to the scientific production during the evaluation period.
The unit declares 96 scientific papers for the period 2016-2021, including 63 peer-reviewed scientific articles among which 25 with UMRS_1112 members in a leading position, eleven additional 'position papers', and 22 clinical reports in peer-reviewed journals. Note that during the analysed period, the hospital practitioners of the unit were co-authors of a total of 180 clinical papers (not all cited in the document). The unit publishes between ten and twelve original manuscripts per year. Cumulated citations are over 1000 in 2021.
Two papers regarding the identifying of novel genes were published in highly competitive journals (Nat. Comm 2016, Embo Mol Med 2020), and five manuscripts concerning phenotype-genotype correlations in retinopathy and ciliopathy were published in good speciality journals. Three papers refine understanding on molecular grounds of DNA repair/transcription diseases. Three manuscripts develop novel bioinformatics tools, and data collection tools. Regarding the 63 scientific articles, 61 concern axes 1 and 2 concern Axis 2. The two manuscripts from Axis 2 report the identification of a novel retinal drug delivery systems (Pharmaceutics 2021), and the mechanisms for diabetes based from data issued from Älstrom syndrome models (Diabetes 2021). The leader of axis 2 has five patents licensed to ALMS Therapeutics (cf. non-academic activities section).

Weaknesses and risks linked to the context

The scientific production is quite satisfactory given the fact that almost all the researchers have heavy clinical and teaching assignments. The limited number of full-time researchers (2 at present and 1 for next term) is nevertheless still a risk for the scientific activity of the unit.

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

All the doctoral students and postdoctoral fellows have published papers (between 1 and 6) and contributed to the scientific production of the unit. Researchers also extensively contributed to publications, often as last or corresponding authors.
Regarding international collaborations, the unit describes collaborations with medical experts and scientific collaborators. This includes collaborations with Germany, Finland, India, UK, Japan, Belgium, Lithuania, the USA, Brazil, and Australia.
There were four patents and the settlement of one start-up for Axis 2.

Weaknesses and risks linked to the context

The number of publications is unbalanced between the two research axes. Axis 1 has multiple publications but not patent, while Axis 2 has several patents, but few published manuscripts. This is due, on the one hand, to an important difference in terms of the workforce, which did not improve during the previous mandate, and, on the

other hand, to the important investment of one researcher in the creation of a start-up. It should be noted, however, that the current organisation will not be maintained in the next term.

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

The scientific production of the unit complies with the principles of research integrity and access to Lagburu electronic laboratory books. The production respects human beings, including large collections with consent forms from the patients and the declaration to the CPP. Preclinical testing has level 1 or level 2 authorisations for experimental procedures and approval of the regional ethics committee on experimentation: 3/4 are currently approved and one is pending. The production of the unit respects the principles of open science, and 74/96 papers were published in journals with open access schemes.

Weaknesses and risks linked to the context

No real identified weaknesses.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

Interactions with the non-academic world are excellent as illustrated by the development of a spin-off company, the obtaining of several patents and interactions with society through numerous radio and television interviews. Of importance, the pivotal role of the unit in the scientific community centred on rare diseases is nicely illustrated by the writing of numerous guidelines and recommendations for various bodies linked to rare diseases.

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

Strengths and possibilities linked to the context

Non-academic interactions are only linked to Axis 2. Noteworthy, Vincent Marion founded in 2017 a spin-off biotech company, ALMS Therapeutics, which is scheduled to enter clinical phase in the US in 2023. In addition, the leader of axis 2 has obtained four maturation grants from Satt Conectus, four contracts with industry, and he has filed seven European and US patents. Five patents have been delivered and licensed to ALMS Therapeutics.

Weaknesses and risks linked to the context

The nonacademic interactions are mostly linked to Axis 2 and should be equilibrated within the unit and reinforced for Axis 1. The unit hosted only one student fully funded by non-academic partners and did not host professionals from nonacademic entities.

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

Strengths and possibilities linked to the context

The creation of a spin-off company and the filing of five patents attest to the vitality of the leader of axis 2 and his propensity to interact with non-academic partners. Further, fourteen documents have been released by members of the unit (8 as lead authors) consisting in writing guidelines, consensus statements, or recommendations on the diseases studied. This is exceptional and attests the recognition of the unit as a key actor in the field of rare diseases and their potential for activities of expertise and support for public policies.

Weaknesses and risks linked to the context

None identified.

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 unit's involvement in interactions with the general public is excellent. Members of the unit participate in meeting with patients' associations. The unit is also often solicited by the media (Rare Diseases Day). The PI has conducted multiple press interviews (32 during the 2016–2021 period), either radio interviews, TV interviews or public webinars. Vincent Laugel has performed seven outreach activities, and the unit has also organised visits of the laboratory for students (3 visits have occurred within the period under review).

Weaknesses and risks linked to the context

No weaknesses identified. Interactions with the society are adequate for a rather small unit.

C - RECOMMENDATIONS TO THE UNIT

Recommendations regarding the Evaluation Area 1: Profile, resources and organisation of the unit

With respect to the scientific strategy, it is recommended to maintain the cohesion of the research topics developed within the unit, in particular from the point of view of the associated clinical aspects. This is currently the case with the pathologies affecting primary cilia, on the one hand, and DNA repair/transcription, on the other hand, which shares sensory impairments and intellectual deficiencies. The addition of a theme on intellectual disabilities related to chromosomal abnormalities is very logical regarding the abilities of the unit, including a clinical reference centre. Furthermore, this axis will be greatly reinforced by the forthcoming arrival of three new researchers (1 MCU-PH, and 2 PU-PH). In contrast, the adequacy of the theme on the genetics of infertility is much less obvious, especially from the point of view of the clinical aspects, and this theme is for the moment carried by only one researcher.
The committee also recommends that the translational activity, which occupies an important place in the identity and strategy of the unit, be revived after the probable departure of one researcher. One possibility would be to refocus efforts on therapeutic approaches to treat retinopathy.

Concerning the unit's organisation, the committee acknowledges the efforts made by the unit to reinforce its permanent technical staff, and of the insufficiency of the results obtained in relation to the needs. Nevertheless, it appears that in addition to this chronic weakness of the technical staff, which causes work overloads and harms the quality of life at work, a lack of clarity in the organisation of the work also generates a certain disarray among these personnel. It would therefore be important, in consultation with all the staff, to clarify this organisation and to involve the researchers as much as possible in the day-to-day management of projects.
In the same way, it seems crucial to quickly appoint a new deputy director with whom the PI and head of the unit will be able to work efficiently and delegate part of her responsibilities, in order to better ensure the continuity of the unit's management.

Recommendations regarding the Evaluation Area 2: Attractiveness

The committee encourages the members of the unit to continue their excellent work while remaining focused on the topics for which they have an internationally recognised expertise and a strong synergy with the clinic. Many efforts to attract new researchers and technical staff were made during the previous term through mobility, which was successful in many cases. The committee can only encourage the unit to pursue these efforts in the future to provide the unit with the necessary means to develop its research objectives.

Recommendations regarding Evaluation Area 3: Scientific Production

The scientific production of the previous mandate is excellent. The committee recommends that this dynamic be maintained and that the unit continue to invest in fundamental work in order to publish in top-level journals.

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

With the planned termination of Axis 2, most of the translational activity of the unit, which was an important part of the previous project, will disappear. As already stated above, the committee encourages the development of other translational projects.

CONDUCT OF THE INTERVIEWS

Date

Start: Thursday October 20, 2022, at 8:15 a.m.

End: Thursday October 20, 2022, at 5 p.m.

Interview conducted: online

INTERVIEW SCHEDULE

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 Hélène Dollfus (20 + 10 min questions)
Attending: EC, SO, all the unit members

Presentation of the Axis

9 h 15 – 9 h 40 Axe 1.1 : Ciliopathies and rare syndromes (Hélène Dollfus, Jean Muller)
(15 min presentation + 10 min questions)
Attending: Team members, EC, SO, director of the Unit

9 h 40 – 10 h 5 Axe 1.2 : DNA repair (Vincent Laugel, Nicolas Le May)
(15 min presentation + 10 min questions)
Attending: Team members, EC, SO, director of Unit

10:05-10:30 Axe 2: Innovative developments (Vincent Marion)
(15 min presentation + 10 min questions)
Attending: Team members, EC, SO, director of Unit

10:30-11:00 Break – Closed session with EC and SO

11:00-11:30 Researchers and professors
Attending: Researchers except group leaders, EC, SO

11:30-12:00 Thesis students and postdocs
Attending: PhD students and postdocs, EC, SO

12:00-1:30 p.m. Lunch Break

1:30 p.m.-2:15 p.m. Technical and administrative personnel
Attending: Technicians, Engineers, Administrative staff, EC, SO

2:15 p.m.-2:30 p.m. Break – Closed session with EC and SO

2:30 p.m.-3 p.m. Meeting with the representatives of Inserm and University

Attending: exert committee, representatives of Institutions, SO

3 p.m.-3:30 p.m. Break – Closed session with EC and SO

3:30 p.m.-4 p.m. Meeting of the Committee with the head of the unit
Attending: Unit Direction, expert committee, SO

4 p.m. – 5 p.m. Meeting of the Committee – Finalisation of the report (closed hearing)

GENERAL OBSERVATIONS OF THE SUPERVISORS

Université de strasbourg

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

Strasbourg, le 22 mars 2023

Objet : Rapport d'évaluation DER-PUR230023241 – LGM – Laboratoire de génétique médicale

Réf. : RB/FF/2023-195

Rémi Barillon
Vice-Président Recherche, Formation doctorale et Science ouverte

Affaire suivie par :
Florian Fritsch
Responsable du département Administration de la recherche et accompagnement des chercheurs

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cher collègue,

L'université de Strasbourg vous remercie ainsi que tous les membres du comité HCÉRES pour le travail d'expertise réalisé sur l'unité de recherche « Laboratoire de génétique médicale » (LGM - UMR_S1112).

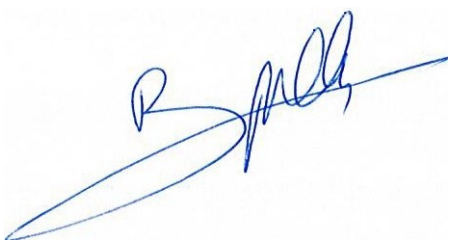
Vous trouverez ci-dessous les observations formulées dans le cadre de ce rapport :

> Page 10, concernant le passage suivant : *« Moreover, if the installation of the unit in its new premises is global/y an excellent opportunity, it has caused delays in recent years and continues to do so, since the CRBS animal house is not yet operational. This involves a camp/ex organisation* for *work with mice, and wi/1 cause further delays in the future when the animals are final/y moved. »*

The old facility, walking distance from CRBS has been maintained during the construction of the new facility, allowing for a continuity of activities. In addition, exceptional funding was obtained by the University from the Ministry of Research and has been provided to the CRBS research units to outsource some of the mice lines in the past 2 years. The construction of the new mice facility has now been finalised and the veterinary approval has been issued as of March 2023. The transfer of animals will be starting this March 2023 and a schedule has been implemented for the facility to reach full operational status by July 2023.

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

Rémi Barillon



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