Research evaluation

EVALUATION REPORT OF THE UNIT

GenLab - Childhood Genetic Diseases / Maladies génétiques d'expression pédiatrique

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

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

EVALUATION CAMPAIGN 2023-2024
GROUP D

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High Council for evaluation of research and hgher education

In the name of the expert committee :

Juliette Azimzadeh, Chairwoman of the committee

For the Hcéres :

Stéphane Le Bouler, acting president

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

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

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

MEMBERS OF THE EXPERT COMMITTEE

Chairperson:	Ms Juliette Azimzadeh Centre national de la recherche scientifique - CNRS, Paris
Experts:	Ms Celine Hernandez, Paris Saclay (representative of the supporting personnel) Mr Didier Lacombe, Centre hospitalier universitaire de Bordeaux - CHU, Bordeaux Ms Servane Tauszig-Delamasure, CNRS, Lyon (representative of CSS Inserm) Ms Estelle colin, Centre hospitalier universitaire d'Angers - CHU Angers (representative of CNU)

HCÉRES REPRESENTATIVE

Marie-José Stasia

REPRESENTATIVES OF SUPERVISING INSTITUTIONS AND BODIES

Didier Samuel, Inserm
Elisabeth Angel-Perez, Sorbonne Université
Emmanuelle Genin, Inserm

CHARACTERISATION OF THE UNIT

- Name: Childhood Genetic Diseases
- Acronym: GenLab
- Label and number: UMR-S 933
- Composition of the executive team: Mr. Serge Amselem, current contract, Mrs. Irina Giurgea, next contract

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

UMR_S933 Inserm/Sorbonne Université Childhood Genetic Diseases (GenLab) is a single-team research unit devoted to the study of rare diseases (RDs) of genetic origin. The three main classes of RDs that are studied are respiratory diseases (primary ciliary dyskinesia or PCD, interstitial lung disease or ILD), autoinflammatory diseases, and developmental diseases (including intellectual disabilities, growth disorders and infertility). The research work aims at identifying both the causes and pathological processes involving these diseases.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

GenLab was established in 2009 at the Armand Trousseau pediatric hospital in Paris, and has been under the direction of Serge Amselem form the start.

RESEARCH ENVIRONMENT OF THE UNIT

The unit shares its premises with the laboratories (UF or Unité fonctionnelle) of Molecular Genetics and Chromosomal Genomics of the Trousseau hospital, which are both reference laboratory (LBMR – 'Laboratoire de Biologie Médicale de Référence') dedicated to diagnosis, prevention and counseling, as well as data collection for research purposes. The three entities collaborate very closely, with most of the GenLab members being also active within the UFs. In addition, GenLab collaborates with several national reference centres for rare diseases (CRMR – 'Centre de reference maladies rares'), two of which are headed by members of the unit (CRMR RespiRare – Rare respiratory diseases and CRMR for patients with Turner syndrome and patients with premature ovarian insufficiency).

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

Catégories de personnel	Effectifs
Professeurs et assimilés	6
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	7
Sous-total personnels permanents en activité	**15**
Enseignants-chercheurs et chercheurs non permanents et assimilés	4
Personnels d'appui non permanents	17
Post-doctorants	0
Doctorants	4
Sous-total personnels non permanents en activité	**25**
Total personnels	**40**

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

Nom de l'employeur	EC	C	PAR
SORBONNE UNIVERSITÉ	7	0	2
Inserm	0	1	4
AUTRES	0	0	1
Total personnels	**7**	**1**	**7**

GLOBAL ASSESSMENT

GenLab's scientific objectives, focused on rare diseases of genetic origin, in particular respiratory, auto-inflammatory and developmental diseases, are excellent. The unit's project takes advantage of the very close integration of the unit's activities with the Molecular Genetics and Chromosomal Genomics UFs, in which the unit's researchers are very active and which are national reference centres for several of the pathologies studied by the unit.
The unit's resources are outstanding, thanks once again to its integration into the hospital environment, as well as its ability to secure financial resources (ANR, Horizon 2020, Labex funding, Programme d'investissements d'avenir, etc. as well as industrial contracts). One issue is that the unit's work generates high-throughput sequencing data for the analysis of which there are not enough expert personnel – at present, only one bioinformatics engineer on a fixed-term contract is involved in data analysis.
The unit's functioning is excellent, and its members have expressed a high level of satisfaction with working there. The different categories of personnel emphasised the strong involvement of the director and senior researchers in supervision and career advancement. The unit could nonetheless benefit from having a scientific advisory board, which is not the case at present.

The unit's attractiveness is excellent to outstanding, with numerous invitations to international meetings (32 in France and 36 internationally), editorial responsibilities in several scientific journals, and numerous participations in expert committees. Most of the unit's researchers are involved as coordinators in national healthcare networks for rare diseases and centres of reference, and are members of European reference networks or coordinators of European societies. In terms of human resources, the unit is also very attractive overall, even if the number of permanent researchers remains low. The unit has trained ten PhD students and hosted two post-docs and several international students – one of whom was subsequently recruited as an Inserm engineer.

The unit's scientific output is excellent, with 212 scientific articles, including 72 signed as first and/or last author and/or corresponding author by members of the unit (including high-level journals such as Nat. Commun., J. Allergy Clin. Immunol, Arthritis Rheumatol, Mol. Psychiatry, Am. J. Hum. Genet, Eur. Respir. J.). Numerous national and international collaborations have also led to the publication of excellent articles in widely read journals (Nature communications, New England Journal of Medicine, Acta Neuropathologica, Hepatology). There is strong interaction between the unit's researchers, who have co-authored numerous articles. The unit has also published 64 reviews, twelve book chapters, 34 editorials or letters, five original articles as participants in a study group, eight didactic articles and ten PNSD (Protocoles Nationaux de Diagnostic et de Soins).

The unit's involvement in society is excellent, with particular emphasis on communication with healthcare professionals and patients, through the production protocols for diagnostic and care ('Protocoles Nationaux de Diagnostic et de Soins', PNDS) and participation in events organised by patient associations. The unit is also actively involved in the popularisation and dissemination of science, as well as in teaching and student life.

DETAILED EVALUATION OF THE UNIT

A – CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

—The previous report first recommended increasing the number of foreign members. This has been taken into account with the recruitment during the previous mandate of two foreign postdocs, one Erasmus student and one engineer.

—There was a concern that the funding had dropped at the end of the previous contract and thus might be insufficient for the next contract. However, a H2020 funding for auto-inflammatory disorders of 1M€ has been secured, as well as several other funding (ANR, AAP Sorbonne Université, PIA Sorbonne Université Labex GenMed, Labex Transimunum,..). Overall, this has increased the budget compared to the last contract, a budget that has remained stable since 2018.

—It was recommended to increase the transfer of results, for instance, by obtaining patents or developing more public/private partnerships. No patents have been obtained but the unit is involved in the RaDiCo program, which results from a public-private partnership. Furthermore, the unit is very active in the direct transfer of their research into diagnosis and patient care through the laboratory of Molecular Genetics.

—The fact that the whole unit is attached to the same doctoral school was deemed problematic for the recruitment of PhD students. To circumvent these limitations, the unit has recruited medical and pharmaceutical PhD students, whose funding is independent of the doctoral school.

—The previous panel was concerned that a large part of the unit funds was pooled, and that there was no secretary to help with fund management, especially given the important workload of the unit director and senior researchers. However, the unit is a single team, and the different projects rely on common equipment, reagents and consumables. Pooling the funds thus seems appropriate. In addition, a management secretary has since been recruited.

—A lack of space was pointed in the previous report, which has not seen a positive evolution beyond an extension of 100 m2 that took place in 2018. A further extension is planned as part of the launch of the Institut des pathologies du développement de l'enfant et de l'adolescent, which will involve moving the unit and the laboratory of molecular genetics to the Pitié-Salpêtrière hospital, but the date is not yet known.

—Another concern was that most researchers are also involved in teaching and clinical activities, with only one full-time researcher in the unit at the time. Another full-time Inserm researcher joined the unit in January 2022, and two other researchers will, however, join the unit in 2025: an Ear, Nose and Throat specialist with expertise on primary ciliary dyskinesia, and a child psychiatrist studying the genetic factors predisposing to early-onset psychiatric disorders. Moreover, two unit's researchers who were hospital practitioners obtained an HDR, another one is applying for a MCU-PH position, and three permanent research supporting personnel and a secretary manager were recruited. This will contribute strengthening the research activity of the unit, either directly or by allowing other researchers to devote more time to their research.

—One last concern was that the unit's future project should take into account the fact that the International Rare Disease Research Consortium was planning on identifying all disease-causing genes by 2020. This has not hindered the scientific production of the unit during the past contract, however, because in-depth investigation remains necessary to identify the disease-causing variants from WGS data. Also, part of the unit's activity focuses on unconventional molecular defects, such as somatic mosaic mutations, which are not the scope of the IRDIRC project.

B – EVALUATION AREAS

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

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

Assessment on the scientific objectives of the unit

The unit's scientific objectives focused on identifying the molecular bases and pathophysiology of rare genetic diseases are excellent.

Assessment on the unit's resources

The unit's resources are outstanding, thanks to its close integration with the hospital environment, in particular with the Department of Molecular Genetics, and its success in attracting funding.

Assessment on the functioning of the unit

The unit's functioning is excellent, both in terms of organisation and quality of working conditions.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

The unit works on rare diseases of genetic origin. The unit's project has three main axes: 1/respiratory diseases (primary ciliary dyskinesia and interstitial lung diseases), 2/auto-inflammatory diseases, 3/developmental diseases (intellectual disabilities, growth disorders and infertility). The project is a continuation of the previous mandate. The environment of the unit is excellent for translational research and the unit is leader for their themes. In particular, the unit's project makes the most of its very close integration with the Molecular Genetics and Chromosomal Genomics UFs, which are national reference centres for several of the pathologies studied by the unit. In line with the unit's scientific project, achievements are published in high-profile journals aimed at both basic scientists and clinicians (Nature Communications, Journal of Allergy and Clinical Immunology, Arthritis and Rheumatology, Molecular Psychiatry, American Journal of Human Genetics, European Respiratory Journal, etc.).

Weaknesses and risks linked to the context

No major weaknesses or risks, but there will be a notable change in unit's direction as Serge Amselem, who has headed the unit since 2009, will be replaced by Irina Giurgea in the new 'Childhood genetic diseases' project.

2/ The unit has resources adapted to its activity profile and research environment, and makes use of them.

Strengths and possibilities linked to the context

U933 comprises a research laboratory that has 150 m² of workspace, and shares 386 m² with the Molecular Genetics UF, stimulating translational research. The unit also collaborates closely with the Chromosomal Genomics UF hosted in the same building, and with the national reference centres for rare diseases (CRMR). Two CRMRs are coordinated by members of U933. The unit also coordinates and manages several platforms located at the Trousseau hospital: molecular biology, imaging, rare disease expertise, RaDiCo (Cohortes Maladies Rares). The high-throughput sequencing platform at Trousseau Hospital is managed by a member of U933. The unit also collaborates with other SU platforms located outside the Trousseau hospital (proteomics, genomics, cytometry).
The unit comprises eighteen permanent active members and eight non-permanent lecturers, researchers and associates. The team includes one CRCN, one PU, four PU-PH, one MCU-PH, three PH, one AHU, one Patt, three emeritus professors, two postdoctoral researchers, two PhD students, and eight engineers/technicians. This represents a total of 10.1 full-time equivalent positions, and eleven scientists have an HDR.

From 2017 to 2022, average funding ranged from €432,000 to €459,000. Two new ANR grants (a 3-year grant on FMF, total 264 k€; a 2-year 'young researcher' grant on auto-inflammatory diseases, total 240 k€), and H2020 funding (as project partner, 1 million for the unit) are secured for the next contract period.

Weaknesses and risks linked to the context

The number of full-time researchers is still low, with only one Inserm CRCN for eleven professors and/or hospital practitioners.

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

Strengths and possibilities linked to the context

The organisation of the unit include weekly lab meetings, and bimonthly unit meetings for presentations and discussions. The Laboratory Council meets once a year. The unit is very committed to promoting career advancement, and the record for the unit's personnel during the previous mandate in this respect is excellent. Students and postdocs are very satisfied with the supervision they receive from the unit's researchers. Overall, personnel expressed great satisfaction with their working conditions and the quality of interactions between unit members, and all emphasised the Director's availability and caring attitude.
The data management plan is adequate from the point of view of traceability and IT security, and there is a business continuity plan.

Weaknesses and risks linked to the context

The frequency of Laboratory Council meetings is low. There is no Scientific Advisory Board.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The unit's attractiveness is excellent to outstanding, with an attractive scientific reputation, as demonstrated by invitations to numerous international conferences and contributions to scientific expertise committees. The unit is strongly involved in the quality of its staff hosting policy, which enabled it to improve the status of four of its researchers. It was successful in competitive calls for projects: one project, H2020, three PIA, and three ANR. The unit is attractive for the quality of its equipment, which is supervised by qualified staff.

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

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

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

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

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

Unit members have been invited to many international meetings (36 outside France, including 17 in Europe), including three times in: the Gordon Research Conference in 2017 and 2019, the European Respiratory Society

(ERS) Congress in 2017, 2019 and 2021, the 32nd European Congress of Pathology and XXXIII International Congress of the IAP in 2020. Unit members have also been invited in France to many (32) meetings and symposia. During this last mandate, unit members organised four workshops (GDR Cil Summer School, CRC BEAT-PCD training school, 4th BEAT-PCD Conference and 5th PCD Training School) and two international virtual meetings (ERS international congress, PCD Foundation Scientific Conference). Members of the unit also took part as chair of two workshops in the ImmunAID meeting in 2022 and 2023 and discussion leaders at the Gordon Research Conference in 2017 and 2019. Unit members hold or have held many editorial responsibilities in internationally recognised journals and collections (Editorial board member for Cells, Biochemical Pharmacology; Academic Editor for Cancers). Members of the unit also participate in several scientific expertise committees, such as the National Committee of French Universities in Genetics (CNU) since 2017 and the Strategy and Research Committee (CSR), Medical School, SU, between 2014 and 2022. Since 2022, the Inserm specialised scientific committee CSS2 – Oncology and Genetic diseases; the Strategy and Research Council (CSR) of the Faculty of Medicine, SU; the Hcéres evaluation committee; the Clinical Research Collaboration (CRC) chILDEU of the European Respiratory Society (ERS). Members also were or are leaders of scientific expertise committees, such as Vice-Dean Research, Medical School, SU between 2015 and 2022; or Leader of the work package 'Genomics' of a European research program (H2020) on Autoinflammatory disorders since 2020. The majority of the permanent researchers who are university hospital practitioners are involved as coordinators in national rare disease healthcare networks (RespiFIL) and reference centres such as those for rare lung diseases or rare endocrine disorders. They are also members of European Reference Networks (ERN-lung) or coordinators of a European Society (the European Respiratory Society).
The unit is intensely involved in training students (10 M1, 16 M2). The unit trained ten PhDs, of whom three are still ongoing. All Ph.D. students trained during the current evaluation period find employment after the completion of their thesis. The unit has also hosted eight international mobility, two Postdocs (2-year-period), and four Greek students in the frame of an exchange. During this last mandate, it also welcomed one visiting scientist from Peking Union Medical College, Beijing, China, during a PhD exchange. The staff hosting policy encourages communication and collaboration while also ensuring that everyone is focused on achieving the same primary objectives. It has an open-door policy and also ensures that personnel have the necessary resources, such as training and mentorship, to perform their jobs effectively. This policy has enabled the unit to recruit an Erasmus student, who was trained in the lab, for an Inserm engineer position. Moreover, the status of three researchers has evolved during the last mandate; two of them were hospital practitioners and passed their HDR; one is PU-PH since 2022, and the other is currently applying for a PU-PH position. The third researcher conducted her research in the framework of a 'Poste d'accueil' Inserm during the previous mandate, and she is currently applying for a MCU-PH position. Furthermore, the unit implements the operational strategy of its supervisory authorities in terms of scientific integrity and open science, as shown by the fact that all its articles are included in HAL. A member of the unit is tasked with systematically uploading scientific output to the HAL portal.
Unit scientists obtained international and European contracts (Partenariats Hubert Curien – PHC – , H2020). The unit is involved in a number of projects funded by 'Programmes d'investissements d'avenir' (PIA), and it carried out three projects financed by 'l'Agence nationale de la recherche' (ANR), of which two are still ongoing. It also obtained grants from a national public agency (Agence de la Biomédecine), a foundation (FMR, fondation du souffle), and an association (Associations Adresh).
The unit is equipped with several platforms, including two for biology and imaging, both located at Trousseau Hospital. It can also benefit from the platforms available within the SU environment. In addition, the unit has two platforms helping to research the medical-scientific environment, which is the rare diseases expertise platform AP-HP. SU, and the RaDiCo (Rare Disease Cohorts) platform. Some of its equipment, including Next-generation sequencing tools (MiSeq, and Next-seq, Illumina), a confocal microscope, Nikon, a High-speed video microscope for ciliary studies, Nikon, and an Affimetrix DNA-chip platform, benefits from a maintenance contract. Each of the unit's equipment is supervised by qualified scientific and technical staff.
The RaDiCo (Rare Disease Cohorts) platform has enabled six industrial partnerships.

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

The unit still has limited space, and it is not certain that it will be moving in the near future.
The unit conducts major research in genetics using high-throughput sequencing technologies, however the lack of bioinformatics staff weakens data processing and therefore the unit's research projects.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The scientific production of the unit is excellent with an impressive list of publications, 324 since 2017 with a broad spectrum of interests going from identification of new disease genes to studies with therapeutic impact. 72 original articles are signed with first and/or last and/or corresponding authorship by the members of the unit. 10 articles target a large audience, among them five excellent journals of specialty. This production represents a great effort of the unit members as a large part has hospital duties. The visibility of the unit is excellent.

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

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

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

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

The scientific production of the unit is excellent with an impressive list of publications since 2017. During the evaluation period, the team has published 212 scientific articles, 64 reviews, 34 editorials or letters, five original articles as participants of study group, eight didactic articles and ten PNSD (Protocoles Nationaux de Diagnostic et de Soins). In addition, twelve book chapters have been written and between the two preprints, one is in revision in eLife.

This scientific production goes from the identification of new disease genes (Thomas, *Am J Hum Genet* 2020, Whitfield, *Am J Hum Genet* 2019, Olcese, *Nat Commun* 2017, Louvrier, *J Allergy Clin Immunol* 2022, Louvrier, *Arthritis Rheumatol* 2023, El Khouri, *Mol Psychiatry* 2021), to study of the impact of specific mutations in SAID (Louvrier, *J Allergy Clin Immunol* 2020, Assrawi, *J Invest Dermatol* 2020, Assrawi, *Rheumatology – Oxford* – 2022), studies with therapeutic impact (Assrawi, *J Invest Dermatol* 2020 ; Louvrier, *J Allergy Clin Immunol* 2020, Frémond, *Thorax* 2020) and phenotype/genotype correlation studies (Legendre, *Eur Respir J* 2020, Cohen, *J Clin Endocrinol Metab* 2017, Cohen, *Hum Mutat* 2019, Donadille, *J Am Coll Cardiol* 2022, Graff, *Hum Reprod* 2020, Portnoi, *Hum Mol Genet* 2018, Peycelon, *J Urol* 2020). This broad spectrum of publications highlights the complementary skills gathered by the unit.

72 original articles are signed with first and/or last and/or corresponding authorship by the members of the unit. ten articles target a large audience. The portfolio highlights five of them (Louvrier *J Allergy Clin Immunol* 2022, Louvrier *Arthritis Rheumatol.* 2022, El Khouri E *Mol Psychiatry.* 2021, Thomas *Am J Hum Genet.* 2020, and Legendre *Eur Respir J*. 2020).

The scientific production is proportionate to the size of the unit and shared between its personnel which is remarkable as most of them have hospital duty. The list of publications highlights a great number of national and international collaborations and consortia which have led to the publication of excellent articles of specialty journals and some with a broad audience (Normand *Nature communications* 2018, Juge *New England Journal of Medicine* 2018, Blanluet *Acta Neuropathologica* 2019, Boelle *Hepatology* 2019 etc.). Of note, there are strong interactions among PIs of the unit which sign multiple shared articles.

The scientific production of the unit complies with the principles of research integrity, ethics and open science with all publications available on HAL. The strong link with the hospitals guarantees the high quality of samples collections, storage and traceability.

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

Some original data have not yet been valorised due to the PI's heavy hospital duties and other responsibilities.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

The unit's inclusion in society is excellent through a wide range of channels, including patient and healthcare practitioner outreach, scientific popularisation and dissemination, open science, teaching and involvement in student life. These activities are aimed at patients and patient associations, as well as the general public and university and high school students.

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

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

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

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

The unit interacts extensively with the non-academic world, particularly in the field of diagnosis and patient care, aimed at healthcare professionals, patients and their families. The members of the unit have contributed 10 National protocols (PNDS) for diagnosis and care during the past mandate (Turner syndrome, inherited disorders of surfactant metabolism, Premature ovarian failure, Acromegaly, Pheochromocytoma and paragangliomas, Pitt-Hopkins syndrome, Mowat-Wilson syndrome, Pediatric hypersensitivity pneumonitis, AA amyloidosis, Pediatric diffuse interstitial lung disease). Members of the unit have also been involved in patient outreach by producing various booklets for patients, parents and professionals. Unit members have interactions with support groups of patients with rare disease (Association française des patients ayant une dyskinésie ciliaire primitive [ADCP], Association Française des Pneumopathies interstitielles de l'Enfant [Afpie], Neuroendocrine cell hyperplasia of infancy [Nehi] France, Association Groupe Amitié Turner [Agat], US PCD patients' support group). They also took part in various outreach events (SU Rare Disease Platform webinar for the Rare Disease Day, webinars for parents of children with neuroendocrine cell hyperplasia, participation to Afpie and ADPC events, Facebook live on Pediatric sarcoidosis, …).

The unit is also well involved in science popularisation and dissemination. Initiatives include an annual participation in a *Conférence des métiers* (Lycée Sainte-Croix, Neuilly-sur-Seine), and twice a year raising awareness of research and related professions among high school student. Members also participate in science outreach events through the 'Fête de la science' or 'Les Festives de Sorbonne Université'. The unit is also clearly involved in disseminating its work through open science activities.

Finally, the unit is present at all levels of teaching activities from the creation of curricula to organisational responsibilities and lecturing. Members of the unit have set up new curricula (Master 2 UE « Medical Genetics and Genomics » SU). They also took part in the creation of exchange programs at the Master level with foreign countries including Australia, USA, Japan and Greece. Members of the unit are responsible or co-responsible of UE for the Science Faculty and Faculty of Medicine ('Medical Genetics and Genomics', 'Medicine and Genomics', 'Human and Comparative Genomics'). Of note, the unit has also set up innovative teaching methods, for instance the Flipped classroom scientific papers critical analysis, and e-learning programs (with the university of Athens). The unit is also involved in student's life, as a member of the unit is Vice-Dean Students' and campus life (Faculty of Medicine, SU) including organisation of workshops and career forum with another member, Vice-Dean 'déléguée internationalisation des formations'.

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

Activities linked to the economic world are absent, but this is mainly due to the general orientation of the Unit.

ANALYSIS OF THE UNIT'S TRAJECTORY

Overall, the achievements of the past period are well in line with the project proposed at the end of the previous observation period. This project was focused on several key aspects: 1) to identify causative genes of rare diseases using the patient cohorts that have been constituted by the unit's members and their network of collaborations over the years (Pulmonary diseases such as PCD and ILD, autoinflammatory diseases such as SAID, infertility linked to POI or chromosomal rearrangements, and developmental diseases such as growth disorders) and to explore the impact of somatic mosaicism in some of these disorders (POI and AID; 2), to develop new approaches for phenotype analysis, such as the analysis of ciliary beating patterns and cilia-generated flow in PCD models, or the search for serum markers for improving the diagnosis of SAID; 3) to develop disease-specific models for PCD, ILD and AID using primary cell culture models; 4) to design functional studies; and 5) to open new therapeutic avenues.

For the next contract, the unit will continue investigating the physiopathology of rare diseases, with a focus on developing projects at the interface between themes. This will involve for instance searching for common genes causative of SAID and ILD, or PCD and infertility.
The unit will continue relying on the patient cohorts and strong diagnostic procedures, expertise in genomics, direct involvement of clinicians in the research, multiple collaborative networks, as well as its capacity to develop experimental models for cell biology that has worked very well in the past. It will also rely on cutting-edge technologies (single-cell sequencing, droplet-based microfluidics) to investigate further the disease mechanisms.
Projects that will be deployed include using WES and WGS on two cohorts of AID patients or to identify mutations linked to Neuroendocrine Cell Hyperplasia of Infancy. Other projects will seek to identify diagnostic markers and potential therapeutic targets for SAID using droplet-based microfluidics, investigate the role of O-linked N-acetylglucosaminylation in SAID. For the study of PCD, the model of primary culture airway epithelial cells developed by the unit will be used to functionally study genes involved in the pre-assembly of axonemal dynein and identify their targets using proteomic approaches and to analyse of the roles of transcription factors controlling multiciliogenesis. The correlation between DNA methylation and phenotype severity in X-linked non-syndromic PCD will also be investigated. For the study of growth disorders, the role of morphogens, in particular Gli2, will be analysed. A search for new POI genes in patients with chromosome translocations will also be implemented, and phenotype/genotype correlation and evaluation of the risks for liver abnormalities in POI patients will be investigated. Finally, the sperm selection process developed during the past contract will be extended to other chromosomal abnormalities and to men with a normal karyotype to evaluate the interests in terms of pregnancy and live birth rates.

The arrival of two new researchers will lead to the development of new research themes. The first project will aim to identify genetic factors linked to chronic rhinosinusitis with nasal polyps, a common feature of PCD that is also widely present in the general population. It will be led by an Ear, Nose and Throat PU-PH who already collaborates with the unit and will join in 2025. In addition, a specialist of clinical and genetic aspects of child psychiatric disorders will move from the Pitié-Salpêtrière hospital to the new Institute of Child and Adolescent Developmental Pathologies that will be hosted at the Trousseau hospital. She will join the unit to study how genetic variants identified from a cohort of childhood or early-adolescent-onset schizophrenia contribute to the development of the disease.

In terms of interactions with the non-academic world, the future project is still strongly focused on patient care (sperm selection procedure for patients with chromosome abnormalities, identification of disease genes and biomarkers for early diagnosis of RDs, identification of potential therapeutic targets such as signalling pathways).

S. Amselem will be stepping down as director of the institute and the next term will be led by I. Giurgea, which will ensure continuity in the direction of the unit and its research themes.

Of note, the future project still involves teaching, directed in particular to physicians and medical students. It will involve the organisation of workshops and seminars directed at doctors and physicians that will focus on the identification of rare molecular variants (already implemented in the course module 'Medicine and Genomics'). A course in Medical Genomics and Genetics for the Master 2 program 'Genetics and Epigenetics' of Sorbonne Université will also launch in 2023.

RECOMMENDATIONS TO THE UNIT

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

There is only one CRCN in the unit, and one goal of the unit for the next contract would be to recruit scientific researchers.
It would also be beneficial to increase the frequency of Laboratory Council meetings to two-three per year. Finally, the appointment of a Scientific Advisory Board would enable the unit to continue to reflect on its long-term scientific objectives, which is important for maintaining the cohesion of scientific themes within the unit.

Recommendations regarding the Evaluation Area 2: Attractiveness

The committee recommends resolving the lack of space while maintaining the interaction between the various members of the unit, which has proved to be a strength to date. It seems that there is still some uncertainty as to whether the unit will be moved or resized.
Another recommendation, of which the unit's members are well aware, is to recruit a bioinformatician to carry out the post-analytical phases essential for high-throughput sequencing and the team's various research projects.

Recommendations regarding Evaluation Area 3: Scientific Production

No specific recommendations.

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

No specific recommendations.

CONDUCT OF THE INTERVIEWS

Date

Start: 19 October 2023 at 8 a.m.

End: 19 October 2023 at 5.30 pm

Interview conducted: on-site or 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

8:30–8:40 Presentation of the EC to the staff members by SO

8:40–9:15 **Presentation of the unit by Serge Amselem and Irina Giurgea** (25 + 10 min questions)
Attending: EC, SO, all the unit members

9:15–11:30 **Presentation of the Axis**
Attending: Team members, EC, SO, director of the Unit

9:15–9:55 **Axe 1: Respiratory diseases**
Primary ciliary dyskinesia (PCD) (Marie Legendre)
(15 min presentation)
Interstitial lung diseases (ILDs) (Nadia Nathan)
(10 min presentation)
(PCD and ILD: 15 min questions)

9:55-10:20 **Axe 2: Systemic auto-inflammatory diseases (SAIDs) (Irina Giurgea)**
(15 min presentation + 10 min questions)

10:20-10:40 **Axe 3: Developmental diseases (Frédéric Lezot)**
(10 min presentation + 10 min questions)

10:40-11:00 **Conclusion (Irina Giurgea)**
(10 min presentation + 10 min questions)

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

11:30-12:00 **Researchers and professors**
Attending: Researchers except group leaders, EC, SO

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

1:30 p.m.-2 p.m. **Thesis students and post-docs**
Attending: PhD students and postdocs, EC, SO

2 p.m.-2:45 p.m. **Technical and administrative personnel**
Attending: Technicians, Engineers, Administrative staff, EC, SO

2:45 p.m.-3:30 p.m. **Break–Closed session with EC and SO**

3:30 p.m.-4 p.m. **Meeting with the representatives of Inserm and University**

Attending: expert committee, representatives of Institutions, SO

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

4:30 p.m.-5:30 p.m. Meeting of the Committee–Finalisation of the report (closed hearing)

PARTICULAR POINT TO BE MENTIONED

N.A

GENERAL OBSERVATIONS OF THE SUPERVISORS

SORBONNE UNIVERSITÉ

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

à

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

Paris, le 16 février 2024

Objet : Rapport d'évaluation GenLab - Childhood Genetic Diseases / Maladies génétiques d'expression pédiatrique

Cher Collègue,

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

Irina Giurgea et Serge Amselem tiennent à souligner la qualité de l'analyse réalisée par le Comité de visite et remercient les membres du Comité pour le temps consacré à cette évaluation et leurs propositions.

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

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

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

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