

EVALUATION REPORT OF THE UNIT
MCPN - Mécanismes centraux et périphériques
de la neurodégénérescence

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

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In the name of the expert committee¹ :

Philippe Marin, Chairman of the committee

For the Hcéres² :

Thierry Coulhon, President

Under the decree n° 2021-1536 of 29th November 2021:

¹ The evaluation reports "are signed by the chairperson of the expert committee". (Article 11, paragraph 2);

² The president of the Hcéres "countersigns the evaluation reports established by the expert committee and signed by their chairperson." (Article 8, paragraph 5).

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

MEMBERS OF THE EXPERT COMMITTEE

Chairperson: **Mr Philippe Marin, CNRS, Montpellier**

Mr Alain Buisson, Communauté Université Grenoble Alpes, Grenoble
(representative of CNU)

Experts : Ms Mounia Chami, Inserm, Paris (representative of Inserm CCS4)
Mr Denis Jabaudon, Université de Genève, Suisse
Ms Suzanne Lesage, Inserm, Paris (representative of PAR)

HCÉRES REPRESENTATIVE

Mr Giovanni Stevanin, Inserm, Paris

CHARACTERISATION OF THE UNIT

- Name: Mécanismes centraux et périphériques de la neurodégénérescence
- Acronym: MCPN
- Label and number: Unistra/Inserm UMR-S1118
- Composition of the executive team: composition of the executive team

SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement

SVE5 Neurosciences et troubles du système nerveux

CSS4 Neurosciences Inserm

CNU69 Neurosciences

THEMES OF THE UNIT

The 'Central and Peripheral Mechanisms of Neurodegeneration' (MCPN) unit (UMR-S1118 Inserm/Unistra) is composed of a single Inserm/Unistra research team. On December 31, 2021, the team counted around 30 persons, including eleven tenure researchers (4 Inserm researchers - 3 DR and one CRCN-, 5 Unistra professors/associate professors and 2 hospital practitioners), three tenure technicians/engineers and five with short-term contracts, six non-permanent researchers or postdocs and four PhD students.

The unit's research topic is entirely focused on the understanding of the genetic causes and pathophysiological mechanisms of two closely related and currently incurable neurodegenerative disorders, amyotrophic lateral sclerosis (ALS) and fronto-temporal dementia (FTD), with the aim of identifying new diagnostic and prognostic biomarkers and innovative therapies. To achieve these goals, the strategy of the unit relies on two main approaches.

First, the unit develops and analyses ALS and FTD animal models (ALS/FTD gene FUS, CHMP2B or VAPB ALS genes) for mechanistic studies based on an integrative approach combining cell biology, imaging, metabolic, electrophysiological and behavioural studies. Second, the unit uses clinical samples and datasets for genetic studies thanks to its longstanding collaboration with a German Institute (DZNE Ulm site), which has been recently established as an 'International research program partner' by Inserm, and its commitment in the French ALS community. At the interface between animal models and clinico-genetic research, the MCPN unit is also implementing iPSC-based approaches through established collaborations with major centres working on iPSC-based models in ALS.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The MCPN research unit was created in 2012 as a follow-up of a previous laboratory (UMR-S692, 2005–2011) called 'Molecular Signalling and Neurodegeneration'. The research topic of this former unit, initially dedicated to basic mechanisms of neuronal death, progressively focused on Amyotrophic Lateral Sclerosis (ALS) to become the core of the expertise of the current MCPN unit together with the overlapping disease Fronto-Temporal Dementia (FTD). For this reason, the unit director logically proposes to rename the future unit as 'Motor Neuron Disease and Associated Dementia' for the next contract.

The unit is located in downtown Strasbourg within the campus of the Faculty of Medicine of the University of Strasbourg (Unistra), at the 4th floor of the Centre for Research in Biomedicine of Strasbourg (CRBS) building.

RESEARCH ENVIRONMENT OF THE UNIT

The MCPN is well inserted in its academic ecosystem. In particular, the unit is part of the Centre for Research in Biomedicine of Strasbourg (CRBS), a federative organisation gathering ten research units in a unique building and developing multidisciplinary research in various fields covering neuroscience, immunology, infectiology, genetics, regenerative medicine, metabolism, cancer and biomaterials.

Interestingly, the CRBS hosts an imaging platform of 400 m² surface that provides its users with a dozen imaging systems of various modalities, such as three recent confocal imaging systems. These systems allow multi-scale observations, from the whole small animal to subcellular scale, in fixed and living samples (video microscopy). The platform is also equipped with various bioinformatics tools for image processing and analysis (IMARIS, Fiji/ImageJ, ICY, iLastik). In addition, a functional exploration platform of 1500 m² surface will be open soon at the CRBS. It will include a conventional animal facility and a pathogen-free sector (SPF), both dedicated to housing and maintenance of rodent lines, as well as a breeding area for zebrafish.

These technical facilities are managed by a service unit (UMS38, also headed by the MCPN unit's director) that is also in charge of several shared services, including a 'laundry' service and an informatics service, as well as a

building operation and maintenance service. This service unit also hosts a 'General Affairs, Management and Administration' supporting service which provides the hosted research units (including MCPN) with a set of administrative and financial management resources.

The unit also has full access to transgenesis, transcriptomics, electron microscopy, viral production and flow cytometry facilities at the IGBMC (Institute of Genetics and Molecular and Cellular Biology) and the ICS (Institut Clinique de la Souris) in Illkirch (suburb of Strasbourg).

The unit is deeply committed to the Strasbourg Idex Site, mostly through two excellence initiatives. It is a founding member of the 'Institut Thématique Inter-disciplinaire' (ITI) NeuroStra (the unit's director is a member of its executive committee) and a founding member of the graduate school Neuro3P, funded by the Idex of Strasbourg University and the SFRI (structuration de la formation par la recherche dans les initiatives d'excellence). The unit's director is responsible for one of the teaching sessions of this graduate school.

The unit has been awarded by Inserm an International Research Program (IRP) entitled 'Metabolic entry points in ALS', which allows access to clinical research samples and projects in collaboration with the DZNE Centre from Ulm (Germany).

In terms of education actions, the unit is a member of the cross-border network 'Neurex' by the way of its training initiatives (PhD students, a tri-national Master's degree, the doctoral program Erasmus Mundus Neurotime), which encompasses the Neuroscience Federations of Basel (Switzerland) and Freiburg-im-Breisgau (Germany). Finally, the unit is a member of the Fédération Hospitalo Universitaire Neurogenycs, and of the 'Fédération de Médecine Translationnelle de Strasbourg' (FMTS) that gathers the laboratories involved in translational research.

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

Permanent personnel in active employment	
Professors and associate professors	2
Lecturer and associate lecturer	5
Senior scientist (Directeur de recherche, DR) and associate	3
Scientist (Chargé de recherche, CR) and associate	1
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	3
Subtotal permanent personnel in active employment	14
Non-permanent teacher researchers, researchers and associates	5
Non-permanent research supporting personnel (PAR)	5
Post-docs	1
PhD Students	4
Subtotal non-permanent personnel	15
Total	29

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

Employer	EC	C	PAR
Université de Strasbourg	6	0	1
Inserm	0	3	2
CHU Strasbourg	1	1	0
Total	7	4	3

UNIT BUDGET

Recurrent budget excluding wage bill allocated by parent institutions (total over 6 years)	525
Own resources obtained from regional calls for projects (total over 6 years of sums obtained from AAP idex, i-site, CPER, territorial authorities, etc.)	118
Own resources obtained from national calls for projects (total over 6 years of sums obtained on AAP ONR, PIA, ANR, FRM, INCa, etc.)	4,973
Own resources obtained from international call for projects (total over 6 years of sums obtained)	137
Own resources issued from the valorisation, transfer and industrial collaboration (total over 6 years of sums obtained through contracts, patents, service activities, services, etc.).	693
Total in K€	6,446

GLOBAL ASSESSMENT

The research topic of the MCPN unit is well focused on two overlapping diseases, ALS and FTD, and relies on the use of cutting-edge technologies. Taking advantage of the creation of original mouse models of these diseases, the unit has provided major insights into ALS and FTD pathophysiology over the last five years. These include

- i) alteration of acetylcholine receptor expression at neuromuscular junction (NMJ) and of NMJ morphology in mutant FUS mice;
- ii) the toxicity not only in motoneurons but also in muscles of mutant FUS mice,
- iii) the early degeneration of corticospinal neurons in ALS and their deleterious influence on the pathology;
- iv) the role of impaired RNA metabolism and translation in early dysfunction of corticospinal neurons;
- v) the role of noradrenaline in the early cortical hyperexcitability observed in different models of the disease and the role of the serotonergic system loss in ALS-associated spasticity;
- vi) the impact of weight loss in ALS
- vii) the identification of NUP50 as a new gene associated with ALS.

Overall, the research made by the unit led to 103 publications over the 2016–2021 period, including an impressive number of papers signed as first/last/corresponding author by the team members published in renowned generalist or speciality journals, such as *Nature Neuroscience*, *Nature Communications*, *EMBO J (2)*, *Neuron*, *Brain*, *Annals of Neurology* or *Acta Neuropathologica (2)*. This scientific production is outstanding in the qualitative and quantitative point of view and relies on an efficient network of international collaborations relative to the size of the unit (>10), often with renowned institutions (for example UCSD, Harvard, ETH Zurich, K.U. Leuven, Max Planck Institute, DZNE). In particular, the unit has a longstanding and fruitful collaboration with the DZNE Ulm site (20 common publications over the evaluation period). The interactions between the unit and the Strasbourg University Hospital are more limited, but this did not impact the unit's projects, as it has access to clinical samples and datasets through its collaborations within the French and German ALS communities. However, increasing the interactions with local neurologists will probably benefit future therapeutic trials.

The impact and renown of the team's research are outlined by

- i) the constant increase in the overall citations per year of the unit's publications (> 800 citations over the period);
- ii) the large number of invited conferences at international congresses delivered by the unit's members (>25);
- iii) the participation of the unit's members in scientific expertise bodies at international, European and national levels and their winning of several scientific prizes and awards, such as 'Prix Coup d'Elan' from the Bettencourt Schueller Foundation (2019), 'Prix Espoirs en Tête' from the Rotary/Fédération pour la Recherche pour le Cerveau (2019), the Eliane and Gérard Pauthier prize (2017) and the FRM Fabrice le Mouaher Prize (2019) ;
- iv) the excellent attractiveness of the unit, which recruited two tenure young scientists and ten postdocs over the period (4 from abroad);
- v) its impressive capacity to raise funding from various national and international institutions or charities (ERC starting grant, 2 ANR PRCI in collaboration with German labs, 5 ANR PRC grants including three as coordinator, AFM – n=4 – , ARSALA, etc.)
- vi) and the label 'FRM team' obtained by the unit in 2016. Increasing the recruitment of young researchers from abroad may be an objective for the future of the unit.

The unit also showed an excellent capacity to train young scientists, especially PhD students (14 PhD theses defended over the period, 4 ongoing). Importantly, the large majority of PhD students and postdoctoral fellows trained by the unit have published articles, with at least one as first author, and some of them have received prizes or awards at conferences (Journées Recherche SLA, ENCALS).

The unit has regular collaborations with private companies and has filed six patents during the period, and one of them is being negotiated for licensing. There was no participation to start up companies even if the results of the unit are probably of interest for their translation in clinical practice.

Members of the unit are regularly participating in lay audience events and are strongly involved in knowledge diffusion, especially toward young people (for example, Kids university). They are active on social media (twitter) and have been participating in various mediatic events (for example, *La semaine du Cerveau*, *La Fête de la Science*, *Rotary Club...*). Overall, the contribution of the unit's research activities to society is excellent.

All in all, the MCPN laboratory is an outstanding unit, which is well managed and well integrated in the local neuroscience community and has full access to state-of-the-art equipment and technologies. The unit has a leading position in the field of ALS in France and Europe and does not suffer from any major weakness.

DETAILED EVALUATION OF THE UNIT

A – CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The unit has successfully fulfilled the most important recommendations raised during the previous evaluation.

Recommendation #1: It would be desirable to maintain the quality of the unit's publications, so far with major publications of a satisfactory Impact Factor (IF) of 10.4. In 2015 IF reached an average of 6.3.

Over the 2016–2021 period, the unit has published more articles in high-ranked journals with the unit staff at leading positions (first, last or corresponding, PDC), such as *Nature Neuroscience*, *Nature Communications*, *Annals of Neurology* (2), *Brain*, *Molecular Neurodegeneration*, *Progress in Neurobiology*, *Acta Neuropathologica* and *EMBO Journal* (2).

Recommendation #2: The team should keep recruiting young and senior full-time researchers as well as postdoc researchers.'

Within the last term, the unit recruited several senior postdocs, one tenure Inserm researcher and one tenure Unistra associate professor.

Recommendation #3: 'The committee of experts recommends to further expand collaborations with companies. As already initiated by the team (see new clinical trial on hypercaloric enteral nutrition) it would be beneficial to strengthen the translational efforts and to bring further clinical-scientific interactions to life.

The unit has significantly expanded its relationships with companies, either through collaboration (Cifre PhD fellowship), collaborative contracts (Domain Therapeutics, Spedding solutions, Coave, Inflectis) or maturation projects with the SATT (Domain Therapeutics, Coave). In addition, the unit has strong relationships with clinicians at the national and European levels. The unit obtained a PIA3 funding for a large ALS cohort, which should boost translational research.

Recommendation #4: The committee of experts recommends to further develop the website of the unit to make it more user-friendly.

The website of the unit is functional but must still be updated. A link to the unit's website can be found on the CRBS website.

Recommendation #5: It is recommended to keep on the momentum and increase the critical mass to reinforce the research in ALS/FTD but also expertise that is not present in the team but mandatory for the proposed project. It is recommended to re-enforce in vitro studies to cover genes involved in ALS/FTD.

The unit recruited a tenure researcher, who has a strong expertise in cell biology and *in vitro* studies to cover this topic.

B – EVALUATION AREAS

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

Assessment on the unit's resources

The MCPN unit has all the necessary human and financial resources to conduct its own research. Compared to the previous contract, the unit reinforced the pool of its permanent researchers by the recruitment of one lecturer of Unistra and one Inserm researcher bringing to eleven the number of Tenure PIs. Six of them hold the HDR, showing the capacity of the unit to train a large number of PhD students (14 theses defended during the evaluated contract period and 10 postdoctoral fellows hired). On the contrary, the unit lost two permanent positions among the technical staff (currently 3 permanent and 5 on short contracts) but this is partially compensated by the access to the local platforms in the new local unit of services. In addition, the unit reinforced its success in grant applications, particularly in competitive European (ERC Starting grants) and French (7 ANR) calls. This shows the full financial operating autonomy of the unit.

Finally, the unit also benefits from a remarkable fundamental and clinical network of national and international collaborations (>10, e.g. with German DZNE, Ulm). Overall unit resources are excellent.

Assessment on the scientific objectives of the unit

The research topic of the MCPN unit is entirely dedicated to the understanding of the genetic and physiopathological mechanisms leading to ALS/FTD diseases and to the identification of biomarkers and new therapeutic targets. The scientific objectives are ambitious but well focused on few subthemes (genetics of ALS, weight loss in ALS, models and therapeutic approaches mainly focused on FUS-ALS), and realistic with regard to the expertise of the staff of the unit and its excellent work environment at the CRBS, where it has access to technological platforms, and benefits from common administrative, financial and informatics management resources.

Assessment on the functioning of the unit

Functioning of the unit is excellent. In accordance with the principles of human resource management, the principal investigators of the MCPN unit have a clear and open policy to value the skills of people with respect to gender equity and without any ethnicity, religion or disability discrimination. The unit is aware of the working conditions of its staff, and is active in the prevention of psychosocial risks through internal discussions. During the last Covid-19 crisis, the team was capable to quickly implement anti-Covid sanitary measures regarding the home office, physical distancing, mask wearing and activity continuity plans, by promoting teleworking, videoconferences and reducing the number of people in the premises. Laboratory council with elected officials and weekly meetings are set up to improve dialogs and internal lab life. The unit applies the recommendations of environmental risk prevention by reducing waste and striving to sort recyclable waste. It uses the Inserm electronic laboratory book that is regularly checked by the supervisors and complies with the protection of scientific assets and computer systems through secured storage at Strasbourg data centre.

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

Strengths and possibilities linked to the context

One major strength of the MCPN unit is its inclusion in the CRBS which is dedicated to advancing research in various domains, including Neuroscience and thus giving access to its powerful technological and animal facilities, as well as common administrative, financial and informatics management resources.

In addition, in spite of its relatively small size (30 persons including 14 permanent staff), the team was capable of producing an impressive amount of high-level papers (>80) and filling six patents, one being more advanced for licensing to Coave Therapeutics, as well as three maturation projects. Moreover, the unit has demonstrated an impressive capacity to raise funding (an average of 800 k€ funding per year) from foundations or patient associations as well as national and European agencies. These successes are due to the high quality research performed by the unit, the participation of the permanent researchers to national and international clinical networks (>10) and the partnership of the unit with four private companies.

Weaknesses and risks linked to the context

A weakness of the MCPN scientific work is its lack of close interaction with the local university hospital that would facilitate the transfer of fundamental research to clinical development in the future.

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

Strengths and possibilities linked to the context

The MCPN unit is a mixed Inserm/Unistra research unit that is internationally recognised for its expertise in ALS. Most of its activities are dedicated to fundamental research, the remaining to educational programs, technology transfer and partnership with industries and research assistance and strategy. The unit is tightly committed to the Strasbourg Idex Site through two excellence programs: the scientific ITI NeuroStra and the educational Neuro3P. The unit shows a great networking activity to ensure the feasibility of its scientific project

as demonstrated by its implication as a member of >10 fundamental and clinical networks and diverse institutions, like the cross-border network 'Neurex', FHU Neurogenycs, FMTS. The unit is also close to the IGBMC and the ICS institutes, facilitating scientific interactions and access to a large set of core facilities. In addition, it is the forward-looking policy of the unit to participate in different national and international clinical projects, like FILSLAN, PULSE, FG-COALS. Three PIs are also members of the advisory boards of charities (ARSLA, ARISLA, AFM). Therefore, the MCPN unit is able to produce scientific knowledge thanks to its local environment and scientific connections for the benefit of the ALS community.

Weaknesses and risks linked to the context

There is an imbalance between permanent scientific staff regarding their contribution to scientific, social, economic and cultural activities of the unit. This imbalance may be explained by an important contribution of some of them in administrative tasks, teaching and hospital practice.

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 MCPN unit complies with the regulations on human resources management, with respect to gender equity, religion, ethnicity and disability. In terms of daily life and lab organisation, the team has striven to set up regular internal meetings and the laboratory council with the attendance of elected representatives from the different staff categories. Regarding staff training, career development or internal mobility, PIs have set up annual interviews for tenure and contractual technical staff and postdocs, which has contributed to the hiring of two young tenure researchers. Postdoctoral fellows and PhD students have been recommended to specific complementary training, particularly in bioinformatics. All people working on animals have been strongly recommended to hold authorisations to work on live animal models with special training in surgery. The relocation of the unit to the CRBS has provided enough space to its current activity and has allowed to get access to network and computer facilities, including secured data storage at the Strasbourg data centre. In terms of health safety, the unit implemented a business continuity plan to cope with any emergency situations, in particular during the last Covid19 crisis where sanitary measures have been quickly put in place to preserve the health and safety of all the staff. The team is aware of reducing waste and sorting recyclable waste.

Weaknesses and risks linked to the context

The committee found a slight imbalance between the number of permanent technicians/engineers (n=3) and that of tenure researchers (n=11), which certainly leads to a pooling of time and expertise of this category of technical staff and then probably work overload.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

Overall, the MCPN unit is attractive at the national and international levels. Its attractiveness is shown by

- i) its capacity to attract early career scientists (10 postdocs, including 4 from abroad, trained over the evaluation period);
- ii) the large number of invited conferences delivered by the unit's staff (>25);
- iii) the participation of the unit in the organisation of major international/European congresses (for example NeuroFrance and First French German and Swiss Congress on ALS/FTD);
- iv) the editorial responsibilities of the unit members in internationally recognised journals and collections and their participation in scientific expertise bodies at European (i.e.: MND association/UK, the ARISLA/Italy and FWO/Belgium) and national (i.e.: French Inserm Neuroscience Panel) levels
- v) and their winning of various international, European and national scientific prizes and awards (Prix Coup d'élan)/Bettencourt Schueller foundation, prix «espoir en tête 2019»/Rotary/Fédération pour la recherche sur le cerveau, Radala Award, Eliane and Gérard Pauthier prize, Fabrice le Mouaher Prize).

In addition, the unit is involved in national and European cohorts/clinical programs and in particular, it was awarded an ANR-PIA3 grant for the French-German ALS cohort, FG-COALS that clearly recognise the investment of this unit in translational research. Finally, the unit has a critical role in training of students and postdocs in the field of Neuroscience and in ALS/FTD in particular and the unit director has an open policy regarding the development of the PI's own research which allowed new projects to emerge in the field such as the project granted by an ERC Starting Grant.

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

Members of the MCPN unit are frequently invited to give lectures at international institutions and congresses (> 25 invitations during the previous contract period). The unit has been involved in the organisation of two international meetings (NeuroFrance 2021 and First French German and Swiss Congress on ALS/FTD). In addition, the members of the unit are involved in regular reviewing for internationally recognised journals and collections (such as *Nature Communications*, *Brain*, *Acta Neuropathologica* or *Annals of Neurology*, >40 articles over the last 5 years). They take part in research steering or scientific expertise bodies at international (ERC, MND association in UK, ARISLA in Italy and FWO in Belgium) and national (ANR, ARSLA, AFM, French ALS association, Inserm Neuroscience panel) levels. The members of the unit won various international, European and national scientific prizes and awards (the 'Prix Coup d'élan' from the Bettencourt Schueller foundation, 'Espoir en tête 2019' from the Rotary/Fédération pour la recherche sur le cerveau, Radala Award, Eliane and Gérard Pauthier prize, and Fabrice le Mouaher Prize). Notably, six PhD students and postdocs of the unit were awarded for their oral presentations at national and international congresses (e.g. Journées Recherche SLA, ENCALIS).

Weaknesses and risks linked to the context

The committee did not identify major weaknesses regarding the international reputation of the unit except that only four of the postdocs were from abroad in a total of ten postdocs hired in the contract period.

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

Strengths and possibilities linked to the context

The MCPN unit regularly attracts early career researchers. One Inserm researcher joined the unit and ten postdocs were trained over the evaluation period with the long-term goal of recruiting them on permanent positions. Two of them applied for such position during the last five years. The unit has regular contacts with young researchers who are potential candidates to join it in the next years.

The unit also trained eighteen PhD students during the last contract. PhD students are integrated within the local doctoral school to attend training courses, and take part in weekly lab meetings in English. Except one resignation of a PhD student, all the PhD students and postdoctoral fellows trained at MCPN for more than one

year have published articles, with at least one as first author. This shows the quality of the training by research provided by the unit.

Weaknesses and risks linked to the context

The committee did not identify major weaknesses even though its attractiveness for early career researchers from abroad was insufficient (4 of the 10 postdocs) and there was no invited researchers during the previous contract. There seems to be some level of inbreeding with regard to the recruitment of permanent staff.

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 MCPN unit was able to regularly obtain significant grant supports to fund its research (6.45 M€ euros during the contract period). This is clearly excellent in regard to the size of the unit (11 PIs). In particular, the committee noted that unit members were granted from competitive European calls, such as one ERC Starting grant (1.5M€), two ANR/PRCI grants with Germany and five ANR/PRC. Among the seven different ANR projects of the unit, three are coordinated by local PIs. The unit also received the prestigious FRM team label in 2016. The unit is involved in national and European cohorts/clinical programs and in particular, it was awarded an ANR-PIA3 grant for the French-German ALS cohort, FG-COALS that clearly recognise the investment of this unit in translational research.

In addition, to increase its visibility, the unit routinely publishes raw data along with the studies, and opts for open access whenever possible.

Weaknesses and risks linked to the context

The unit was granted at the European (ERC, ANR/PRCI) and national (ANR/PRC, foundations) levels. There is the lack, however, of the coordination of a multicentric international consortium on ALS/DFT since the only internationally funded projects are mainly bicentric with German colleagues.

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

Strengths and possibilities linked to the context

The unit has developed a know-how in molecular and cell biology to perform most of its own research locally or with the help of local facilities. In addition to classical molecular biology, histology, EEG, electrophysiology equipment, the unit has privileged access to an imaging platform (photonics) equipped with a dozen imaging systems in various modalities, including three recent confocal imaging systems and to a functional exploration platform that comprises a conventional animal facility and pathogen-free sector. It also has access to mass spectrometry, electron microscopy, imaging, flow cytometry, virology, genomics, metabolomics and transgenesis facilities in other campuses located in Strasbourg or its suburb.

Weaknesses and risks linked to the context

The committee did not identify major weaknesses and risks related to the equipment to conduct the MCPN research program but noted that bioinformatics and genetics, one recently implemented aspect of the unit only relies on the work of one single postdoc.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The research axes that have been developed provided major achievements in the field of ALS and FTD. The project results fill the gap of initial objectives stating the lack of understanding of the genetic causes and disease modifiers underlying ALS and FTD, the poor understanding of the pathophysiological mechanisms, and the lack of effective therapeutic options. Over the last five years, the unit produced 103 publications that have collected more than 800 citations.

Overall, this is an outstanding production for eleven PIs. The scientific quality of these studies is demonstrated by their publication in wide readership and historically recognised speciality journals with high quality requirements and revision processes, including *Nature Neuroscience*, *Nature Communications*, *EMBO J*, *Neuron*, *Brain*, *Annals of Neurology* and *Acta Neuropathologica*. This high-level scientific achievement was supported by the establishment of few collaborations with prestigious institutions inside and outside Europe. Notably, the unit shares several key publications (over 20) with the DZNE Ulm site.

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

Strengths and possibilities linked to the context

The impressive production of this relatively small unit (103 publications and 6 patents for 11 PIs) was possible thanks to its policy that leverages multiple complementary approaches, ranging from the development of original ALS and FTD animal models to address specific questions on pathophysiological mechanisms. These innovative models were used to explore behavioural phenotypes, energy metabolism and electrophysiology. This was possible thanks to

- i) the access of the unit to well-equipped local platforms implemented at the CRBS or in other institutes located in Strasbourg or close to Strasbourg (mass spectrometry, electronic microscopy, imaging platform, flow cytometry, virology, omics and transgenesis),
- ii) the acquisition of state-of-the art equipment (Metabolic cages equipped with standard EEG 'Promethion eight cage Set up with DSI EEG', multi-channel EEG recording system and various equipment of imaging 'fluorescent Western blot and molecular biology sonicator),
- iii) And the expertise of permanent researchers and postdocs funded by the unit (e.g.: a postdoc recently brings a novel aspect to the unit on bioinformatics and genetics).

Weaknesses and risks linked to the context

There are some manuscripts signed by the PIs of the unit for which the MCPN affiliation is not properly referenced, which impact the visibility of the unit in various scientific platforms such as Scopus.

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

During the evaluation period, the research unit has significantly increased the visibility of its research in terms of quality (recognised journals) and quantity (103 articles). This is due to the management system of the unit that favour the development of specific research axes of the unit by junior researchers. This will certainly help these researchers for the development of their leadership, scientific recognition and career progression. The specific contribution of PhD students and postdoctoral fellows as first author of publications is also a rule in this unit.

Weaknesses and risks linked to the context

Most of the scientific production is shared among several PIs. There is effectively a lower publication rate of three permanent associate professors of the unit that might result from their heavy administrative and pedagogic duties, which are part of their missions.

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 MCPN unit publishes its articles in highly visible, generalist or specialised journals. Most of these journals are recognised for publishing high quality and large studies spanning from the molecular mechanisms of disease development to the rescue approaches *in vivo*. Importantly, the unit publishes in open access journals, thus increasing its international visibility and recognition. Specifically, the unit publishes in gold open access journals (9 publications). It also publishes in the green open access platform HAL managed by Inserm as well as the BioRxiv and medRxiv platforms.

The unit has implemented Inserm electronic laboratory books that are regularly checked by the PIs.

All studies involving Human samples are conducted with the authorisation of either

- 1) the Committee for the Protection of the Persons (CPP) of the University Hospitals of Strasbourg,
- 2) the AP-HP (Paris Public Hospital System), and under the supervision of the Direction Générale de la Santé (DGS), in compliance with applicable ethics rules.

Clinical research performed in collaboration with Ulm University has been approved by the local ethical committee. The project has direct translational applications through collaborations and transfer agreements, allowing access to human-derived samples and datasets and also by setting up of national cohorts. In addition, the unit is developing iPSC-based models of ALS, thanks to the expertise of a permanent researcher, the recruitment of a young researcher (who will be proposed for a 'chair' position at Inserm) and the collaboration with centres with recognised expertise.

The unit members are also committed to promote the best practices in animal experimentation. One of its members takes part in the local ethical committee for animal experimentation (Cremeas), and another one supervises animal experiments training for all PhD students and researchers at Unistra.

Weaknesses and risks linked to the context

The committee did not identify weaknesses regarding research integrity.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

The MCPN unit stands out by the quality of its non-academic interactions. The unit obtained substantial funding by successfully applying to International and French charities. The researchers of the unit are also strongly involved in scientific mediation. If the unit has strong interaction with companies and a proactive policy to patent results, it did not lead to the creation of any start-up company. In summary, the unit establishes contractual partnerships with the non-academic world and develops collaborative research projects with industry that could be strengthened by the creation of (or participation in) start-up companies. The unit members including PIs, postdocs and PhD students, actively participate in the dissemination of its scientific knowledge and the progress of their ongoing research.

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

Strengths and possibilities linked to the context

The Unit's strategy to develop partnerships with actors in the non-academic world is very successful.

The Unit obtained several grants from international and national charities including AFM (4), Fondation Recherche sur le Cerveau, Fondation pour la Recherche Médicale (FRM Team), three ARSLA grants, and two grants from the Thierry Latran Foundation and one grant from France Alzheimer. The unit hosted a PhD student with a Cifre fellowship (thesis completed on June 21, 2021), in the frame of a collaboration with Domain Therapeutics. This led to one common publication. The research unit has also ongoing proactive policy to patent results of possible socio-economic value in connection with the local SATT Conectus. Even if no start-up has been created during the evaluation period, the unit has filed six patents. One of them is currently being negotiated for licensing to Coave Therapeutics.

The unit's staff have regular contact with private companies and give presentations or consultancies to these companies. During the last contract, they gave a talk at Biogen (Cambridge, MA, USA, 2017), established

consultancies with Braineever (Paris) and served as a member of the scientific advisory board of Cytokinetics (2022). The PI has been participating in a national institutional round table on ALS gathering biotech companies in March 2022 (France Biotech).

The unit is actively involved in ALS patient associations by participating in the scientific board and conferences to promote knowledge on ALS and FTD. Three researchers of the unit are still (or have been) active members of the scientific board of the French ALS association (ARSLA). One of them also participates in yearly board meetings of ARISLA (Italian ALS association) was appointed member of the Inserm neuroscience panel CSS4 (2016–2021), and was then elected for a second term (2021–2025).

The unit regularly participates in scientific mediation events, such as the Semaine du Cerveau, Declic, Fête de la Science (Primary school pupils, 2021) and Top Music (General Audience, 2019). Its staff gave conferences to general audiences (Rotary Club Saverne; Rotary Club Saint Louis; Association couleur Espoir Wittenheim, 2019...). The unit members also participated in the dissemination of scientific knowledge by giving lectures in special events such as AFM-telethon that organised '1000 Chercheurs dans les écoles'. The research unit has a proactive policy in spreading research results to the socio-economic world and the lay public. The unit organises awareness-raising actions for young people. Several PhD students of the unit participated in the 'Kids University'. One of them participated in 'My thesis in 180 seconds', 'Brain Mysteries', 'Week of the Brain', and 'Science Fair'. Several researchers of the unit are active members of the 'Kids University' and are involved in actions in primary schools during the Fête de la Science (Primary school pupils).

The constant collaborative efforts with private companies and the sustained implication of the unit in scientific mediation activities demonstrate a successful cross-linking between the unit's research activities and the non-academic world.

Weaknesses and risks linked to the context

During the period of evaluation, the unit has developed many contacts with several industrial companies which clearly demonstrates the interest of the scientific results for pharmaceuticals, but there has been no creation (or participation in) start-up companies during this period.

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

Strengths and possibilities linked to the context

The MCPN unit has an ongoing proactive policy to patent scientific results of potential socio-economic value. The unit interacts with private companies via the local SATT Conectus. Interactions of the unit with private companies are frequent and efficient. During the evaluation period, the unit has filed six patents. One of them is currently being negotiated for licensing to Coave Therapeutics.

The unit's scientific staff gave presentations or were involved in consultancies for several private companies, such as Biogen (Cambridge, MA, 2017) and Braineever (Paris). The PI served as a member of the scientific advisory board of Cytokinetics (2022) and he has been participating to a national institutional round table on ALS associating biotechs and organised by France Biotech.

Weaknesses and risks linked to the context

If the important number of patents filed by the unit during the evaluation period underlines the constant objective of its researchers to value their scientific and technological resources, the number of licensed or exploited patents is low (one single).

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 MCPN unit's staff strongly invest in sharing with the general public their knowledge on ALS and FTD by participating in patient associations and to broad audience events. They are or have been active members of the scientific board of the French ALS patient association (ARSLA). The PI of the unit is also involved in yearly board meetings of the Italian ALS patients' association (ARISLA).

The unit is also contributing to debates in society by regularly participating in lay audience events ('My thesis in 180 seconds', 'Brain Mysteries', 'Week of the Brain', "Science Fair" and the "Kids University" in elementary schools during the Fête de la Science).

Members of the lab are regularly posting scientific contents related to their research topics and recent publications on social media (twitter). Some of their conferences are available on-line (<https://inc.parisdescartes.fr/fr/2020/09/25-septembre-caroline-rouaux-inserm-u1118-universite-de-strasbourgfrance/>).

Weaknesses and risks linked to the context

The committee did not note any particular weakness regarding to communication with the public and society and encourages the unit to update its website.

C - RECOMMENDATIONS TO THE UNIT

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

The committee recommends the unit to expand its expertise in human genetics in line of the unit scientific project to dissect/understand the physiopathology mechanisms of ALS/FTD and to identify novel genetic causes and biomarkers. Likewise, it recommends that the unit hires a researcher with skills in bioinformatics and big data on a permanent position. The slight lack of permanent technical staff should be reduced by perpetuating the position of the short-term staff thanks to local opportunities with Unistra.

Recommendations regarding the Evaluation Area 2: Attractiveness

The committee recommends the unit to open recruitment more broadly at the level of permanent staff and this starts by the recruitment of more postdocs from abroad.

The committee recommends the unit's director to apply for competitive European grants for the recruitment of talented early-career researchers (for example Marie Skłodowska-Curie Actions), given that the type of funding provided by French agencies such as ANR does not allow the funding of postdoc salaries on the long-term, thus significantly limiting the attractiveness of such positions in France.

Recommendations regarding Evaluation Area 3: Scientific Production

The committee recommends the unit to invest its translational efforts with local and national university hospitals for the genetic and therapeutic-based approaches.

In addition, the committee thinks that the unit should ensure that its affiliation is correctly referenced in its publications to optimise its visibility in various scientific platforms, such as Scopus. The imbalance in terms of production among PIs may be prevented in the future by co-directions of students, for example.

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

The committee recommends the unit to pursue its efforts for the licensing of its patents and to take all opportunities to participate in the creation of start-ups to exploit their findings.

CONDUCT OF THE INTERVIEWS

Date(s)

Start: 17 October 2022 at 9 a.m.

End: 17 October 2022 at 6 p.m.

Interview conducted: on-line

INTERVIEW SCHEDULE

Programme des Entretiens
Mécanismes Centraux et Périphériques de la Neurodégénérescence
Date des entretiens (ZOOM) : 17 Octobre 2022
Directeur actuel du laboratoire : M. Luc Dupuis

Conseiller Scientifique HCERES : M. Giovanni Stevanin

Comité d'experts :

M. Philippe Marin : Expert panel HCERES (Président du comité)

M. Alain Buisson : représentant CNU69

Mme Mounia Chami : représentante CSS4 Inserm

M. Denis Jabaudon : Expert panel HCERES

Mme Suzanne Lesage : représentante Personnel d'Appuis à la Recherche

9 h - 9 h 30 Accueil du comité de visite en huis clos

Zoom link 1 (HCERES) :

<https://hceres-fr.zoom.us/j/91691496007?pwd=cGtQSEdQTm1nZGIUK09HQUIZUVFYZz09>

9:30-9 : 45 Présentation du processus d'évaluation par le conseiller scientifique HCERES (Giovanni Stevanin)

Zoom link 2 (UMR) :

<https://us02web.zoom.us/j/83361422262?pwd=V25KK0tWY25ERmVRWkhJeGpEcFJYdz09>

9:45-12 : 30 **Présentations scientifiques — Zoom link 2**

9:45-10 : 15 Présentation de la stratégie scientifique par le directeur d'unité (Luc Dupuis) (Thématique de recherche, structuration, RH, finances) (15' présentation + 15' discussion)

10:15-10 : 30 *Pause-café*

10:30-12 : 30 Présentations des programmes de recherche (8' présentation + 7' discussion)

10:30-10 : 45 Présentation d'un chercheur en début de carrière (candidat CPJ 2023) : Génomique de la SLA/DFT (Salim Megat)

10:45-11 : 00 Biologie moléculaire et cellulaire de FUS, perspectives thérapeutiques (Chantal Sellier)

11 h - 11 h 15 Physiopathologie de la SLA et DFT FUS, approches par les modèles murins (Raphaëlle Cassel)

11:15-11 : 30 *Pause-café*

11:45-12 : 00 Physiopathologie de la SLA et DFT CHMP2B, approches par les modèles murins (Frédérique René)

12 h - 12 h 15 Rôle du cortex cérébral dans la SLA (Caroline Rouaux)

12:15-12 : 30 Hypothalamus, perte de poids et SLA (Luc Dupuis)

12:30-13 : 00 Débriefing du comité de visite en huis clos — **Zoom link 1**

13 h - 14 h *Pause déjeuner*

14 h - 15 h 30 **Discussions avec le personnel du laboratoire en comités restreints**

Zoom link 3 (UMR) :

<https://us02web.zoom.us/j/83867925969?pwd=RjBob3ArdlNBc1gyazBaTm80WTdaQT09>

14 h - 14 h 30 Discussion avec les chercheurs (sans le directeur d'unité)

Gestion des accès = Raphaëlle CASSEL, MCU Unistra

14:30-15 : 00 Discussion avec les étudiants et Postdocs (sans les chercheurs)

Gestion des accès = Olga ROMAN, doctorante Unistra

15 h - 15 h 30 Discussion avec les techniciens, ingénieurs et administratifs (sans les chercheurs)

Gestion des accès = Stéphane DIETERLE

15:30-15 : 50 *Pause-café*

15:50-16 : 20 Discussion avec le directeur d'unité (huis clos) — **Zoom link 1**

16:20-17 : 00 Discussion avec les représentants des Tutelles (huis clos) et représentants locaux
Zoom link 1

– **Inserm :**

Etienne Hirsch (Inserm, ITMO)

– **Représentants des tutelles locales :**

Valérie Lamour, vice-présidente Recherche déléguée secteur Vie & Santé

Responsable administrative de l'UMS : Nathalie Christophe

Anna Lazar, adjointe au délégué régional

17 h - 18 h Débriefing du comité de visite en huis clos — **Zoom link 1**

18 h *Fin de la journée*

PARTICULAR POINT TO BE MENTIONED

Interview by visio with no issues.

The committee received strong support to this unit from the supervising bodies during the interview.

GENERAL OBSERVATIONS OF THE SUPERVISORS

Université

de Strasbourg

Monsieur Éric 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

Strasbourg, le 24 mars 2023

Objet : Rapport d'évaluation DER-PUR230023303 - MCPN - Mécanismes centraux et périphériques de la neurodégénérescence

Réf. : RB/FF/ 2023-198

Rémi Barillon

Vice-Président Recherche,
Formation doctorale et Science
ouverte

Cher Collègue,

Affaire suivie par :

Florian Fritsch
Responsable du département
Administration de la recherche et
accompagnement des chercheurs
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L'université de Strasbourg vous remercie ainsi que tous les membres du comité HCERES pour le travail d'expertise réalisé sur l'unité de recherche « Mécanismes centraux et périphériques de la neurodégénérescence » (MCPN – UMR_S 1118).

Nous n'avons 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.



Rémi Barillon

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Valorisation**

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