Research evaluation

EVALUATION REPORT OF THE UNIT

LMN - Laboratoire de Maladies Neurodégénératives : mécanismes, thérapies, imagerie

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Université Paris Saclay

Commissariat à l'énergie atomique et aux énergies alternatives - CEA

Centre national de la recherche scientifique - CNRS

EVALUATION CAMPAIGN 2024-2025

GROUP E

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High Council for evaluation of research and highter education

In the name of the expert committee:

Bogdan Draganski, committee president

For the Hcéres:

Stéphane Le Bouler, acting president

In accordance with 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

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M Olivier Lefebvre, direction des sciences du vivant, CEA
M Reiner Veitia, chef de l'institut Jacob, CEA

CHARACTERISATION OF THE UNIT

- Name: Laboratoire de maladies neurodégénératives : mécanismes, thérapies, imagerie
- Acronym: LMN
- Label and number: UMR9199
- Composition of the executive team: Drs Gilles Bonvento et Julien Valette

SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement
SVE5 Neurosciences et troubles du système nerveux

THEMES OF THE UNIT

The Neurodegenerative Diseases Laboratory: Mechanisms, Therapies, Imaging (LMN)'s scientific themes cover the broad spectrum from basic research to pre-clinical and clinical applications, including the mechanisms of neurodegeneration and neuron-glia interactions. The themes converge on genetic, cellular mechanisms and drug therapeutc strategies for neurodegenerative diseases, with particular emphasis on Alzheimer's, Parkinson's and Huntington's diseases. The LMN is composed of 6 teams that focusing on the following 6 themes: 1 - Abnormal protein folding and aggregation in neurodegenerative diseases; 2 - Cellular interactions in neurodegenerative diseases: models and biotherapies; 3 - Reactive astrocytes; 4 - Advanced NMR methods to probe cellular changes in vivo; 5 - Multimodal integrative imaging of neurodegenerative diseases and therapies; 6 - Innovative and translational therapeutics. The collaboration between the teams follows both a transversal axis along the different levels of observation - genetic, molecular, cellular/synaptic, systemic and a longitudinal axis along the three neurodegenerative diseases of interest.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The Neurodegenerative Diseases Laboratory (UMR9199) (LMN) is the continuation of the CEA/CNRS URA2210 unit based at the Service Hospitalier Frédéric Joliot until 2009. The URA2210 unit was created in 2004 and then renewed in 2010 after its first AERES. This was followed by the creation of the UMR9199 unit in 2015. The UMR9199 is affiliated to the CEA, the CNRS and the University of Paris-Saclay. Since 2009, it is located at MIRCen (Molecular Imaging Research Center) on the CEA site in Fontenay-aux-Roses. MIRCen is an 8,500 m^2 preclinical research facility that was initially developed by CEA and Inserm. MIRCen is currently a department of the CEA's DRF (Basic Research Division) and is part of the Institut de Biologie François Jacob, which groups together several CEA departments and services on the Fontenay-aux-Roses site, including IDMIT (Infectious Diseases Models for Innovative Therapies), IRCM (Institut de Radiobiologie Cellulaire et Moléculaire), SEPIA (Service d'Etude des Prions et des Infections Atypiques) as well as the Genoscope and CNRGH (Centre National de Recherche en Génomique Humaine) in Evry. MIRCen is part of the EATRIS European infrastructure for Translational Medicine.

RESEARCH ENVIRONMENT OF THE UNIT

The unit UMR9199 is affiliated to the CEA, the CNRS Biology and attached to the Faculty of Science at the University of Paris-Saclay. Since 2009, it is located at MIRCen, which is part of the EATRIS European infrastructure for Translational Medicine. Through one of the unit's PIs, LMN is leading the National Biology-Health Infrastructure NeurATRIS since 2012 (€31.3 million for the period 2012-2024). Thanks to NeurATRIS funding, MIRCen purchased in 2023 a cyclotron and a radiochemistry platform for production of labelled radiotracers. The LMN teams are involved in the 4 PEPRs of the 'Biotherapies and bioproduction of innovative therapies' national acceleration strategy: iPSC-France, BioScale, QualAAV and EDITO.

UNIT WORKFORCE: in physical persons at 31/12/2023

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maitres de conférences et assimilés	1
Directeurs de recherche et assimilés	12
Chargés de recherche et assimilés	10
Personnels d'appui à la recherche	25
Sous-total personnels permanents en activité	**49**

Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	5
Doctorants	19
Sous-total personnels non permanents en activité	**24**
Total personnels	**73**

DISTRIBUTION OF THE UNIT'S PERMANENTS BY EMPLOYER: in physical persons at 31/12/2023. Non-tutorship employers are grouped under the heading "others".

Nom de l'employeur	EC	C	PAR
CEA	0	11	21
CNRS	0	8	4
U Paris Saclay	1	0	0
Autres	1	3	0
Total personnels	**2**	**22**	**25**

GLOBAL ASSESSMENT

The overall unit's profile is excellent to outstanding given its leading role in neuroscientific innovation at the national and international level. The unit's excellent to outstanding attractiveness is ensured by impressive competitive funding achievements (NeurATRIS, ERC, PEPR, ANR) and unique research infrastructure at MIRCen, combining cutting-edge technology for non-invasive and invasive investigation of the brain from molecular via synaptic and cellular to systems level. The beyond state-of-the-art technological platforms are adequately supported by a highly skilled technical staff, which ensures the exceptional quality of acquired data. The analytical power of the theoretical neuroscientists team is complementing this outstanding research environment. The unit's outstanding research output (Nature Neuroscience, Cell Metabolism) has made major scientific contributions to the characterisation of alpha-synucleins and glia cells in neurodegenerative disorders. The unit has developed and validated a novel positron emission tomography radiotracer sensitive to neuroinflammation and has pushed the boundaries of magnetic resonance imaging-based metabolic imaging at 11.7T focused on the role of glutamate in ageing and Alzheimer's disease. The links to society are excellent to outstanding given the numerous articles in the mass media and involvement in CEAs "open doors" events.

DETAILED EVALUATION OF THE UNIT

A - CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The unit has followed the recommendations from the previous evaluations. The recommended focus on mechanistic studies led to an increase of publications in top-tier journals. Similarly, the unit developed and implemented a mid-term strategy in collaboration with institutions at the Mauritius Island for maintaining the non-human primates research despite increasing pressure through administrative drawbacks brought by European regulations. In addition, the unit was able to increase its visibility to the general public, despite the restricted access to CEA premises due to its specific status. On the same note, the efforts of the unit to attract foreigner researchers should be commended. The recommendation to respond to the unit's engineers and technicians to improve the communication and ensure their stronger implication in research projects was addressed only partially. As recommended, the smaller research groups and promising PIs was given sufficient support such that they could obtain prestigious grants (ERC Consolidator).

B - EVALUATION AREAS

Guidelines for all areas of evaluation (1, 2, 3 and 4): 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 profile is matching in an **excellent to outstanding** way one of the five CEA's strategic objective, namely the topic of technologies for the future medicine. Here, the unit's developments in medical imaging and technologies for disease prevention and diagnosis that are followed by strong research in therapeutic innovations. The breadth of basic neuroscience research covering the molecular and cellular mechanisms of neurodegeneration, validated in animal models including non-human primates is completed by translation in clinical research using novel non-invasive imaging methods.

Assessment on the unit's resources

The financial resources through competitive national and international funding mounting to Euro 8 Mio are **outstanding**. An important income source are the industry service contracts. The unit benefits also from paid contracts with other CEA research units. The NeurATRIS initiative financed the purchase of a cyclotron and radiochemistry laboratory (valued at Euro 10 Mio) in 2023.

Assessment on the functioning of the unit

The unit's functioning is **excellent to outstanding** with a remarkable stability of the research staff counting 11 "directeurs de recherche", 11 "chargés de recherche" and two "enseignants-chercheurs". Similarly, the continuing funding of 25 engineers and PAR (only 4 on short-term contracts) is best suited to support the technological platforms and ensure the maintenance of technological know-how and expertise beyond the evaluation period. The outgoing researchers and PAR (n=13) were adequately replaced by new recruits (n=14).

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

The main objectives to develop a translational research strategy for optimal transfer of knowledge from basic research to clinical trials represent the undisputed strength of the unites scientific approach. During the evaluation period, the unit has brought scientific breakthroughs in the field of transmission of neurodegeneration relevant proteinopathies and in the characterisation of glial cells that resulted in top-tier journals (Cell Metabolism, Nature Neuroscience, Brain, Nature, Nature Metabolism). Similarly, advances in NMR spectroscopy methodology and AI-based tools for histological tissue characterisation ensured the success of past and current ERC grants. The development of the 18F-DPA-714 PET ligand sensitive to neuroinflammatory processes, the unique applications of the CEST-MRI methodology and the successful use of the 11.7T animal MRI complete the basis of an excellent to outstanding scientific portfolio. This secured several ANR (SUMMA), Horizon Europe, ERC, CPER, CPER, PIA and France 2030 projects, patent filing and unique collaborations with industry (AC Immune, DPA-714 monoclonal antibody clinical trial). Similarly, the LMN teams are active participants in the PERP "Biothérapies et bioproduction de thérapies innovantes ». Finally, this led to the leadership in the "Infrastructure Nationale en Biologie-Santé" pro NeurATRIS within the Programme « Investissements d'Avenir » (2012-2024).

The objectives are thematically and operationally well-aligned with the policy of the supervisory authorities. The feasibility of the ambitious objectives put forward is ensured by the unit's scientific strategy combining empirical research with theoretical modelling across all levels of observation - from genes, molecules, synapses to networks and systems. The unique technological platforms and the accumulated expertise by technicians, engineers and researchers are the pillars that carry this strategy. The focus on the most frequent genetic and sporadic neurodegenerative diseases - Alzheimer's, Parkinson's and Huntington's diseases and the aim to translate newest research tools and findings into clinics are the strongest proof for the societal relevance of the unit's strength in this domain. The relevance of the scientific objectives is best exemplified by the leadership on the topic of reactive astrocytes and a strain of own and collaborative publications in top tier journals. Given the breadth of the scientific objectives, the consolidated internal organization in 6 different teams with own themes that are well-integrated at the unit's level, provides the optimal basis for successful operational implementation of the unit's strategy.

Weaknesses and risks linked to the context

The strengths of a broad translational strategy based on research at different scales of observation are at the same time a potential weakness if across between the teams' research topics is not maintained. In the current organizational and thematic construct, there is a fruitful cross-fertilisation across pathologies and spatial scales. In the case of a team leaving the construct, there should be a contingency strategy how to replace the missing links.

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

Strengths and possibilities linked to the context

Despite the constraints on obtaining permanent research positions, the unit has succeeded in recruiting permanent staff from the CNRS and the CEA. The financial resources through competitive national and international funding representing 90% of obtained funds, are outstanding showing a significant increase from Euro 1.9 Mio to Euro 8 Mio for the current evaluation period. This includes an ERC Consolidator Grant (2019-2025), 10 European contracts, 6 of which are supported by the teams, 24 ANR grants, 10 of which are supported by the teams, 4 PEPR-BBTI grants and 30 grants from charities (France Alzheimer, France Parkinson, etc.) and foundations (FRM, Vaincre Alzheimer, etc.). An important income source is the industry service contracts (> 20 contracts, e.g. with Theranexus Servier, UCB and with start-ups - e.g. Axoltis). The unit benefits also from paid contracts with other CEA research units - e.g. the Institut de la Vision that are using the provided infrastructure and know-how. The NeurATRIS initiative spearheaded by the unit financed the cyclotron and radiochemistry laboratory (valued at Euro 10 Mio), to also allow for intra-mural funding of 8 collaborative projects using this infrastructure (Euro 50-100 K/project).

Weaknesses and risks linked to the context

A potential weakness is the fine balance between "service" to commercial enterprises and scientific developments following the unit's strategy. This task is solved in well-adjusted way by the current directorship, but remains a challenge for the future.

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

Strengths and possibilities linked to the context

The created position for a health and safety prevention assistant, the establishment of a Quality of Life at Work unit and the appointment of a responsible for training in all relevant safety, IT and research domains, additionally to an outstanding plan for green transition "GreenCen" have contributed to improving the functioning of the unit. The measures for prevention of sexual harassment, mobbing and discrimination, additionally to the implemented strategies for IP protection and IT security are following the institutional rules and regulations.

Weaknesses and risks linked to the context

The lack of governance strategy in the context of academic affiliations and CEA regulations, carry the potential of authority powers' imbalance between LMN and MirCen. This has also implications for the relative scarcity of adequate communication and interaction between teams (team leaders and staff), which carries the potential of administrative staff's isolation.

EVALUATION AREA 2: ATTRACTIVENESS

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

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

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

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

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

The excellent to outstanding attractiveness builds on the reputation of the unit beyond national borders - the leadership in the National Biology-Health Infrastructure project NeurATRIS, CEA, ANR and European research projects. Similarly, the collaboration with industry partners - Servier, UCB, Wave Life Sciences, Eli-Lilly, Coave Therapeutics helped to increase the visibility of the unit. The unit's attractiveness builds on a rich portfolio of seminars and meetings for scientific exchange at various levels - weekly "MIRCeminars", support for participation in scientific associations - France Parkinson, Huntington France, European HD Network and the first edition of the "Journée Doc et Post-Doc" of the Institut de Biologie François Jacob. Despite the closed environment as CEA unit, LMN attracted three foreign visiting researchers, organised a seminar on "open science" and showcased the skills of young researchers with a dedicated session: 'Next Generation Challenge' at the annual Translational Neuroscience Day by NeurATRIS. Similarly, the unit's researchers gave numerous invited presentations (>100), organised conferences - Jacques Monod, NeuroFrance, EHDN, Brain PET, were elected in international bodies of excellence - Académie Vétérinaire de France, Académie de Médecine, presidency of the Network for European CNS Transplantation and Restoration (NECTAR), were editors at scientific journals (Glia) and participate in strategic research boards (divisions 25 and 28 of the CNRS), charitable foundations - Fondation pour la Recherche Médicale, Fondation Vaincre Alzheimer) and patients' organizations (France Alzheimer, France Parkinson) et de GRD (BioSimia). The unit's attractiveness is supported by the unit's scientific leadership in MR imaging, cell-targeted viral vectors and production of alpha-synuclein assemblies. The unit's unique technological platforms for viral production; cell culture; aptamers; functional explorations; behavioural analyses; radiochemistry; PET imaging; NMR imaging; histology and microscopic analyses and clinical imaging - 2 utra-high field MRI magnets (7T for non-human primates and 11.7T for preclinical research) and two microPET scanners, are contributing to the visibility at the national and international level. The high attractiveness of the units is also due to the outstanding amount and diversity of competitive funding including 24 ANR projects (10 led by the teams), and 30 projects funded by charitable associations (France Alzheimer, France Parkinson, etc.) and foundations (FRM, Vaincre Alzheimer, etc.). There are several European fundings (ERC Consolidator), H2020-IMI and JPND, the Michael J Fox Foundation and the Swiss National Science Foundation (SNSF). The unit has recently been involved in PEPR, with 4 projects funded, including one coordinated by the LMN.

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

Given the geographical and regulatory seclusion of CEA's infrastructure, there are no major weaknesses or risks related to its attractiveness and scientific reputation. A potential weakness is the heavy reliance on high-end MRI equipment that has surpassed the established approximative equipment life span. A major breakdown without contingency plan in place would cause delays in some research programs. The unit has an outstanding strategy to integrate new recruits and accompany the existing staff towards promotion, the unit is successful in competitive nations and international calls, the unique equipment infrastructure is a major factor in ensuring high level of attractiveness.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The overall scientific production of the unit is **outstanding** including publications in top-tier journals with high citations count. The publications cover the broad spectre of the unit's original research supporting highly relevant methodological and applicational work. The majority of articles include PhD candidates, post-docs and technical personnel as co-authors. The publications follow strictly institutional and European recommendations and rules for scientific integrity and open science for research using both animal models and human volunteers.

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 outstanding showcased by own and collaborative work was published in top-tier journals (Nature Neuroscience, Cell Metabolism, Nature Communications, Cell, Nature, Nature Neuroscience, Nature Metabolism, Brain, EMBO Journal, Cell Reports et Stem Cell Reports). Not only the number of publications (n=260) with a significant proportion of first and last authorship (n=101), but also the quality of publications coming from all 6 teams is impressive. The differences in the size of research teams is represented by their proportionally adequate number of publications. It is noteworthy that more than 60 articles are co-authored by PhD candidates, post-docs and technical staff thanks to the implemented policy of voluntary participation in research articles. All publications are conformed with existing regulations for scientific integrity and open science, which are accessible to all LMN members on a dedicated website. All acquired data are safely stored at local servers with access rights that are traceable. Experiments using animal models or human volunteers are subject to ethical authorization by the MESR and the Ethics Committee no. 44, to which the researchers report, in accordance with the existing law, and following the filing procedure set up by the CEA. There is particular attention on animal wellbeing following the recommendations of the structure in charge of animal welfare (SBEA) with 12 individuals representing the LMN at the monthly meetings. The non-human primates' experiments follow similar strategy, with regular exchange of various welfare information at local and national level, including funding for organ sharing (PrimShare).

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

There are no weaknesses or risks pertaining to this area of evaluation.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

The unit's research activities contribution to society is **excellent to outstanding**. This is ensured by the strong translational links with the biomedical sector at national and international level, the transfer of scientific discoveries to other research domains, particularly clinical research, and the agile and thriving communication activity for the grand public despite certain constrains due to the special CEA status.

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

Contributions to society are based on strong links with industry, which will increase from 20% to 30% of LMN's own resources by 2023, coming from around 20 industrial partnerships (Theranexus, Servier, UCB…). Besides the local partnerships with Theranexus, Servier, structure PASREL-Imagerie sur Paris-Saclay, there are several foreign collaborations including ERIC EATRIS and the Michael J Fox Foundation. The partnerships through Cifre thesis agreements (Sanofi, Néoxia) and large-scale frameworks (NeurATRIS, Pasrel-imaging) helps capitalising the acquisition of novel expertise. The societal contributions are visible through the creation of start-ups for AI-based histology evaluation (witsee.ai) or free-ware for ontological evaluation of omics data - http://shiny.imib.es/devea. LMN has also contributed to the creation of national guidelines for prion and SARS-Cov-2 related research at the level of the Ministry of Higher Education and Research. The unit is very active in its interaction with the general public including participation at the CEA event 'Scientifique, toi aussi' including 70 secondary school students discussing career opportunities, similar to a yearly event for secondary school students for their 3rd year work placement. The LMN participates in the open days of the CEA's FAR site and the Brain Week. The main scientific achievements are communicated through the supervisory bodies (CEA, Paris-Saclay and CNRS) in leading popular science journals such as the Edition de l'Université Paris-Saclay, Pour la Science, Ouest-France and Sciences et Avenir.

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

There are no weaknesses or risks pertaining to this area of evaluation.

ANALYSIS OF THE UNIT'S TRAJECTORY

The unit's overall performance across all evaluation areas is excellent to outstanding. In the last evaluation period, the unit has made major scientific discoveries, has secured an impressive amount of competitive funding that allowed for the purchase of a cyclotron and the creation of a radio-chemistry laboratory, has increased its attractivity with several ANR, PEPR scientific projects, and a prestigious ERC Consolidator grant to finally, present its achievements to the general public in the mass and social media, and file for two patents.

The change of leadership of the unit, which followed a major restructuring of the LMN with the creation of new team middle of the Covid period, has overcome many challenges to support the positive development of the unit. However, the major strategic challenge of ensuring a coherence between the LMN and CEA governance systems has not been adequately addressed. The Committee believes that the reasons for this lie beyond the personal qualities and ambitions of the unit's leadership.

At the end of the evaluation period, the CNRS and the University Paris Saclay - Faculty of Science, decided to cease their affiliation with the LMN unit, which consequently led to the partially effectuated exit of CNRS researchers to other academic institutions, notably to NeuroPSI and Neuro-Bicetre. Despite the natural logistic, inter-personal and academic contact-related challenges, the new leadership has managed to overcome these, propose a lean CEA-centred new structure of the unit, which does not carry anymore the governmental ambivalence of previous times.

The new project is promising, but there is a clear need to work towards Inserm affiliation. The evaluation committee strongly supports the affiliation to Inserm and recommends to the supervisory body of DRF-CEA to facilitate as much as possible the current and future initiatives by working with the Faculty of Medicine or/and Pharmacology of the University Paris Saclay, which could maximise the chances of success. In this context, the affiliation to Inserm through the ITMO “techno pour la santé” (technology for health) could lead the unit to become a technology centre.

RECOMMENDATIONS TO THE UNIT

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

Given the unit's major restructuring and the fact that the CNRS and the University Paris Saclay - Faculty of Science, decided to cease their affiliation with the LMN unit at the end of the evaluation period, our recommendations focus on the need to reconsolidate the unit's research objectives and the need to work towards an Inserm affiliation. It is mandatory to finalize on a written unit's governance that will ensure not only the responsibilities of the new two pillars' teams, but will also define top-down and bottom-up communication channels across hierarchies. This will avoid potential conflicts in difficult transition times between PIs, permanent researchers at lower hierarchical levels, postdocs, students and technical staff. The planned exit of CNRS researchers to other academic institutions should be further well-supported and accompanied by the unit's leadership. Particularly important are the continuation of ongoing scientific projects. The evaluation committee strongly supports an affiliation to Inserm and recommends the engagement with the Faculty of Medicine or/a Pharmacology at the University Paris Saclay that could maximize the chances for success.

Recommendations regarding the Evaluation Area 2: Attractiveness

The unit's excellent to outstanding attractiveness could be maintained in the transition phase by keeping the current policy for integrating newcomers and promoting successful unit's members. Here, the planned continuation of ongoing projects and collaborations with the departing CNRS funded colleagues would be also an important milestone. Finally, the swift achievement of an Inserm affiliation leading to renewal of the University Paris Saclay affiliation through the Faculty of Medicine and possibly the Faculty of Pharmacy would be of major importance to keep the unit's attractiveness by integrating several MCH-/PU-PH and reinforcing the translational character of its research.

Recommendations regarding Evaluation Area 3: Scientific Production

The outstanding level of the unit's scientific production should be maintained through the proactive collaboration with outgoing CNRS researchers and establishment of new joint projects. The current strategy following recommendations to focus on mechanistic studies, paid out and this should be continued.

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

The transition towards full CEA affiliated unit should not prevent more activities that will maintain the excellent to outstanding level of the unit's contribution of research activities to society. The unit's achievements in science should be proactively presented in social and mass media channels, individuals' success with major funding (e.g. ERC) should be shared with the grand public. Similarly, the rich portfolio of intellectual property should be valorized through patents or the creation of start-ups ensuring the swift translation of research results to products with impact on humans' health and wellbeing.

TEAM-BY-TEAM ASSESSMENT

Team 1: Protein misfolding and aggregation

Name of the supervisor: Mr Ronald Melki

THEMES OF THE TEAM

The Protein misfolding and aggregation Team 1 focus is on the relationship between the structure of alpha synuclein and tau protein aggregates and their impact on pathology in neurodegenerative diseases such as Alzheimer's or Parkinson's disease. A particular emphasis is set on the molecular mechanisms of protein aggregation and the intercellular propagation of the different forms of aggregates.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

In line with the recommendation of the previous committee to increase the number of PhD students, 10 PhD students were trained during the period with 6 of them already successfully completed, in addition to 6 post-docs. Collaborative work has been performed together with the other teams (including 1 PhD co-direction) leading to a large number of common publications. The previous report mentioned limited interactions with the non-academic sphere. Industrial partnership has been strengthened in particular through the proteomic platform.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2023

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	0
Sous-total personnels permanents en activité	**3**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	0
Doctorants	4
Sous-total personnels non permanents en activité	**4**
Total personnels	**7**

EVALUATION

Overall assessment of the team

The team's overall **excellent to outstanding** evaluation is building on excellent organisation, excellent to outstanding attractiveness that is supported by an outstanding publication record and impressive amount of competitive funding from both national and international funding sources. The team has several projects in European programs combined with a high international recognition of its team leader. The contributions to society are excellent to outstanding.

Strengths and possibilities linked to the context

During the period of evaluation, the team demonstrated the critical importance of the structure of alpha-synuclein and tau aggregates in the development of neurodegenerative pathologies. Starting with tissues from patients, they showed that the structure of the protein aggregates could represent a novel diagnostic tool as it constitutes a barcode determining the characteristics of the pathology and the cerebral tropism. The team also characterized the pathways regulating the cell entry of the protein aggregates and the subsequent steps to cell death. The team published more than 50 original articles in high-ranked journals (e.g. EMBO J, Nature Comm, eLife, Acta Neuropathol) with about one fifth in leading positions and seven review articles in top-tier journals (e.g. Sci Transl Med, The Cerebellum). In particular, each PhD student published at least one article as first author. First author publications by PhD and Post-doctoral researchers represent 13% of the team production. Numerous publications attest to the successful collaborative work with the other LMN teams and international collaborators. The team's international recognition is visible in the high citation number, four keynote invitations in international meetings, the organization of the Conference J Monod in 2022 by the team leader and two lectures in international meetings by two other team members. In addition to the team leader, one member has editorial responsibilities (e.g. Acta Neuropathologica, Experimental and Molecular medicine) and one is member of scientific boards (FRC, Association France Parkinson, Fondation de France). The team leader's expertise is acknowledged by two awards (JiePie, Grand Prix Fondation Simone et Cino del Duca) and participation to international steering committees. He also took part in a committee in charge of safety regulations for work with prion and prion like particles in France. The team is strongly involved in the functioning and methodological development of the Gif Proteomic platform as referent research team. One team member acts as scientific and operational manager. The team secured excellent funding (2.3 M€) as coordinator or partner from European (H2020-IMI IMPRIND, PD-MitoQUANT, Flag ERA Trapp-med, ERA PerMed), international (USA, Qatar) and national (ANR, NeurATRIS, FRM, Vaincre Alzheimer, France Parkinson, AXA) source and from industrial partners (e.g. UCB, Eli-Lilly, Lundbeck, Janssen, Novartis) or as service provider through the proteomic facility. The team is co-inventor of two patents on conformation selective aptamers that enable the detection of alpha-synuclein in liquid biopsies and on artificial intelligence-based analysis of histology images. One team member coordinated a CNRS-Enterprise training course. The team members actively participated in actions towards the general public through communications via scientific organisms or societies but also through a series of YouTube videos and interventions in media. The team's attractivity is showcased by the recruitment of one CNRS researcher and hosting four postdoctoral fellows and eleven PhD students.

Weaknesses and risks linked to the context

The funding relies almost exclusively on the team leader and all high-profile presentations were performed by the team leader. The major implication in the scientific and operational management of platforms, especially the Proteomic-Gif platform, represents a significant work load for the team members. Because the team leader will reach the age limit for retirement, he is not eligible as team leader for the next term. This situation requires to clarify the integration of the three permanent researchers (2 CNRS, 1 Inserm) in the new structure and may have a mid-term negative impact on the follow-up of the scientific projects.

Analysis of the team's trajectory

The team joined the LMN in 2019 and has well integrated its environment. It has successfully pursued its original research line and maintained high international visibility as attested by the publication record and high success rate in securing national and international funding extending beyond the current period of evaluation. However, the team has encountered some managerial difficulties during the period. The team leader's age and the current team composition (two CNRS and one Inserm permanent researchers) raise concerns regarding their integration in the future structure.

RECOMMENDATIONS TO THE TEAM

As the research interests of the team are strongly linked to human pathologies, the team members could consider strengthening the translational aspects and entering into "premature" programs.

Also, the international recognition of the team leader being established, further supporting of career development for the other permanent team members is highly recommended. Maintaining a balance between platform and research management is also particularly important.

Team 2: Cell-cell interactions

Name of the supervisor: Mr Alexis Bemelmans & Mr Anselme Perrier

THEMES OF THE TEAM

The Cell-cell interactions team studies the role of interactions between neurons, glial cells and the immune system in neurodegenerative diseases such as Alzheimer's, Parkinson's or Huntington's disease. The team relies on innovative models and technologies (e.g.: grafts derived from pluripotent cells from non-human primates; modelling of proteinopathies using gene transfer techniques) to understand the role of brain cellular interactions in the pathophysiology of prion-like diseases and to propose innovative therapeutic strategies.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team, led by PIs, allowed the integration of each member of the team, which is in line with previous recommendations. The previous report also highlighted the risk of a very ambitious team project for a small team. Even though the project remains ambitious for a small team, all researchers successfully developed their projects leading to high-impact publications, thus meeting the recommendations of the previous report. However, the team did not resolve the question of the first-author position of doctoral students, since of the twelve students who defended their thesis, only eight are first or co-first authors of at least one article, which means that four students defended their thesis without being the first or co-first authors of their articles. Finally, continuing from the previous report, the team developed relationships with industrial partners.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2023

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maitres de conférences et assimilés	1
Directeurs de recherche et assimilés	4
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	6
Sous-total personnels permanents en activité	**11**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	3
Doctorants	5
Sous-total personnels non permanents en activité	**8**
Total personnels	**19**

EVALUATION

Overall assessment of the team

The team's overall results are **excellent to outstanding** with excellent organisation, excellent to outstanding attractiveness with several international researchers and scores of PhD and postdocs, additionally to an excellent to outstanding publication track record. The team has obtained significant funding from ANR and a European H2020 project to reaffirm its excellent contributions to society.

Strengths and possibilities linked to the context

The team is well established in its field of research and benefits from excellent national and international recognition. Their publications demonstrate original and innovative scientific results in their fields of research. During the evaluation period, team 2 achieved a scientific breakthrough demonstrating that stem cell-derived neurons can form in vitro neuronal networks, providing a relevant model to study the propagation of pathological aggregates between connected neurons (Gribaudo et al., 2019). This followed by another significant finding that the pathological Tau protein can be transmitted from neurons to astrocytes (Maté de Gérando et al., 2021) and evidenced the crucial role of the microglial receptor TREM2 in the elimination of Tau protein aggregates (Vautheny et al., 2021). They actively collaborated with other teams of the unit. Hence, they demonstrated with the team 6 that simple matching of major histocompatibility complexes (MHC) is not sufficient to avoid long-term rejection of grafts from pluripotent cells implanted in the striatum of macaques (Aron Badin et al., 2019). Their work has allowed them high-level scientific recognition, both nationally and internationally. One of the co-directors of the team has been part of the steering committee of the international SC4HD consortium since its creation. This consortium brings together researchers around the theme of cellular therapy for Huntington's disease. The other co-director sits on the scientific council of various associations at national (FRM) and international level (Vaincre Alzheimer, Alzheimer nederland, Alzheimer Forshung initiative). One of the PIs is part of the ERA-NET eRARE H2020 partnership project (TratpolyQ" (2017-2021) and has led the international/Europe pole of CNRSD-biology since 2020. The team publishes regularly (53 articles since 2018) in high-impact journals (3 articles in Brain; 1 review in Cell Metabolism) (32% as first, last or corresponding author), demonstrating excellent visibility of the projects. There is also a strong collaboration with the other teams in the unit, with 13/52 publications coming from inter-team collaborations (with teams 3-4-5-6). The majority of first author publications (70%) are co-authored by PhD students. The team has obtained numerous funding from various sources, including ANR as PI and industrial collaborations (e.g. Theranexus). In particular, the collaboration with Theranexus allowed the equipment of a platform dedicated to the screening of repositionable drugs and high-throughput analysis on functional tests carried out on human neurons and astrocytes. The team also benefited from funding under PIA2030 including 3 PEPR projects which allowed to complete the equipment of the viral production platform. The team also demonstrates its attractiveness through the post-doctoral researchers who has been recruited (since 2018:7 completed + 3 in progress). Finally, it can be noted that the team is made up of full-time researchers and (only) one teacher-researcher. The team also benefits from significant research support with 3 technicians and 3 IEs for 5 researchers/ECs.

Weaknesses and risks linked to the context

The recognition indices of team 2 largely depend on the outstanding performance of one of the PIs with reference to the organization of conferences and responsibilities in learned societies. The previewed departure puts a risk for the team's trajectory. The team has the assets necessary for this recognition. The team is encouraged to engage towards learned societies and to organize national and international conferences. The restructuring of the team must ensure this recognition continuity.

Analysis of the team's trajectory

The team has demonstrated remarkable continuity in the addressed research themes, which allowed to establish a solid national and international recognition. The change in management that took place during this last contract did not impact the quality of the research carried out by the team, once again demonstrating the strength of the team. The team's research domain of expertise – spanning between the astrocyte's role in neurodegeneration, propagation of alpha-synuclein and neuroprotective strategies coupled with lentiviral and AAV vector methods is a promising avenue for the future research projects that supports the notion of a positive trajectory. The ongoing participation in several collaborative projects 3 PEPR (iPS France, QualAAV et EDITO, démarrés fin 2023), the labex REVIVE and NeurATRIS together with R&D initiatives in the industry sector provide a stable basis for the continuation of the long-term research vision.

RECOMMENDATIONS TO THE TEAM

The evaluation committee recommends that the team maintains its international visibility and recognition by maintaining a high impact of publication and an excellent funding politics. Team is also encouraged to engage towards learned societies and to organize national and international conferences. A point of vigilance is brought to the place of students in the authors of their publications. Each PhD student must defend his/her thesis with at least one article in first or co-first position.

Finally, we encourage the team to involve men and women equally in team responsibility tasks (e.g. direction).

Team 3: Molecular complexity of reactive astrocytes

Name of the supervisor: Mme Carole Escartin

THEMES OF THE TEAM

The Molecular complexity of reactive astrocytes team has a strong expertise in the role of reactive astrocytes in various neurodegenerative diseases with a special focus on the JAK2-STAT3 signalling pathway. Their research projects explore the dual role of reactive astrocytes in order to understand both their detrimental effects and their potentially beneficial functions in disease. By developing innovative viral tools and using in vivo models, the team examines how modulation of this pathway influences astrocytic behaviour and impacts neuronal health. This approach aims to increase fundamental understanding of astrocyte biology, but also to identify potential therapeutic targets for several neurological disorders.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team positively addressed the most important recommendations made in the previous Hcéres report. It has successfully maintained an excellent publication record with studies of high quality published in prestigious journals. The team was able to expand by recruiting a young CR, which enhances stability and ensure the development of more ambitious projects.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2023

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**4**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	0
Doctorants	3
Sous-total personnels non permanents en activité	**3**
Total personnels	**7**

EVALUATION

Overall assessment of the team

The team's work on the dual roles of astrocytes in neurodegenerative diseases is evaluated as **excellent to outstanding**. It has gained international visibility to achieve excellent to outstanding attractiveness that secured funding for an engineer and a permanent position for an early career researcher. The outstanding scientific production is paralleled by excellent contribution to society with active involvement in mentoring young trainees and in participating to outreach activities.

Strengths and possibilities linked to the context

The team's scientific production is excellent, with eleven original publications in top-tier journals such as Brain and Acta Neutopathol Commun, along with five review articles, including one in Nat Neurosci, which has highly contributed to the increasing team's international recognition. Team 3 has demonstrated significant scientific achievements through its research contributions. The team has successfully coordinated a consensus article involving over 80 experts from 22 countries, clarifying the nomenclature and definitions related to reactive astrocytes. This effort has positioned the team as a leader in addressing ongoing controversies and identifying future research challenges on these cells. The publication in this prestigious journal positions it as key contributor to insightful discussions in the field. Moreover, the team's research articles, such as those in *Brain and Acta Neuropathol Commun*, reveal the dual roles (positive and negative) of reactive astrocytes in neurodegenerative diseases like Huntington's and Alzheimer's. These publications highlight the capacity of the team to produce high-quality research in prestigious journals. Overall, the team has published 16 articles during the reporting period, including 11 as first or last author, 5 reviews and 9 publications shared with other teams of the unit. All doctoral students have at least one article as (co-)first author and have contributed to writing at least one review. Over the past years, the team has demonstrated a strong commitment to the recruitment and development of students (6 in total) and two post-docs. Notably, one of the post-docs was recruited as a researcher with a permanent position in the team. It has welcomed 10 Master's upon which 3 students from abroad (Denmark, India, and Chile) and two foreigner doctoral students (Argentina and Spain) besides the 6 doctoral students (3 successful completion and 3 ongoing). In addition, the team successfully obtained 13 grants for approximately 860 k€, with 9 of them obtained as coordinators. The grants include 3 ANRs, 8 from national foundations and 1 postdoctoral return-to-France grant from the FRM. The team members also participated to 6 international conferences and seminars enhancing the team's visibility in their scientific community including the inaugural plenary lecture at the Alzheimer's Association International Conference in San Diego in 2022 and the presidency of the Club Français des Cellules Glials. The high level of attractively is also supported by the PIs inclusion in the editorial board of GLIA, a leading journal in the field of glial cells, the Joël Ménard Prize award in 2019 for the basic research on Alzheimer's disease and the membership elect at the Comité National du CNRS (Section 25; 2021-25). The recruitment of a permanent researcher ensures the team's expertise and stability. The team is also actively committed to outreach activities, including its participation in the Brain Awareness Week, FRC Neurodon, and initiatives to support for women in science at Paris-Saclay. For all these reasons, team 3 is well-positioned to continue to contribute significantly to the understanding of reactive astrocytes in various neurological contexts. The team actively engages in non-academic collaborations and outreach activities. The PI established a collaborative contract with the Belgian company UCB (2022–2024). The team has also been involved in public initiatives such as Brain Awareness Week, FRC Neurodon, and programs supporting women in science at Paris-Saclay. Team members have contributed to media interviews (*Pour la Science*, *Science et Vie*) and have authored invited articles in the French journal *Médecine/Science*. The PI is presently vice-president of the French Club of Glial Cells.

Weaknesses and risks linked to the context

While there are no major weaknesses for this team, it could expand its efforts for obtaining financial support from European or international funding agencies or foundations. This could enhance the team's international visibility and facilitate larger collaborative projects.

Analysis of the team's trajectory

Team 3 has shown a positive trajectory in its research output and influence over recent years. The integration of innovative viral tools to selectively modulate reactive astrocytes has opened new avenues for understanding their roles in neurodegenerative diseases like Alzheimer's and Huntington's diseases. Furthermore, the establishment of collaborations with both academic and industry partners, including a project with UCB company in Belgium, reflects the team's growth and acquisition of recognition.

Overall, team 3 is well-positioned to address critical questions in neurobiology and continue its success. The team relocated to NeuroPSI Institute in the summer 2024 and will no longer be part of the LMN unit in the upcoming contract period.

RECOMMENDATIONS TO THE TEAM

The committee recommends that the team maintains its visibility in the international competitive field of astrocytes. The researchers of the team may apply to European and international grants to create or integrate international consortia. Building on a past recommendation, the team could further enhance the clinical and socio-economic valorisation of its research, considering that the team's topic has a significant translational potential.

Team 4: Advanced magnetic resonance to probe brain cell alterations in vivo

Name of the supervisor: Mr Julien Valette

THEMES OF THE TEAM

The Advanced magnetic resonance to probe brain cell alterations in vivo team (team 4) focuses on the use of MR diffusion-weighted spectroscopy to study astrocyte morphology and of MRI-based metabolic imaging, in particular glutamate CEST, to image brain disorders with polyglutamine expansions.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

There were no specific recommendations for team 4 in the previous evaluation besides the common ones referring to the role of technical staff in the research activities of LMN.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2023

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

EVALUATION

Overall assessment of the team

Team 4 hosts unique imaging infrastructure and develops highly original analytical methods. Overall, the team 4's achievements are evaluated as **excellent to outstanding**. The team's outstanding organisation has supported an equally outstanding attractiveness indicated by high capacity at securing competitive international and national fundings, by high visibility on the national and international scientific scene and by hosting of visiting researchers. Team 4's scientific production is excellent to outstanding with excellent contributions to society.

Strengths and possibilities linked to the context

Team 4 has developed three main lines of research at the interface between methodological developments in NMR spectroscopy and neurobiological questions. Diffusion spectroscopy led to impressive results, such as the quantitative estimation of the astrocytic microstructure, and the evaluation of the intracellular-extracellular distribution of cerebral lactate. MRI imaging of oxygen 17 was developed to study cerebral oxygen consumption in rodent models in the APP/PS1 mouse model of Alzheimer's disease. The chemical exchange saturation transfer

(CEST) MRI imaging of polyglutamine expansion diseases has revealed early brain metabolic alterations, particularly in the white matter, and identified relevant biomarkers for the study of these diseases.

Team 4 success is showcased by the receipt of the prestigious ERC Consolidator grant by the PI and the coordinator role in the ANR JCJC nrjCEST and the synImaging project funded by the Fondation de France, additionally to the partner role in ANR PRC TreatPolyQ, ANR PRC Brainfuel and ANR PRC MetaTune. This and other partnerships ensured the budget of Euro 2.3 Mio that secured three PhD thesis and two post-doctoral contracts. During the period, the team indeed trained nine PhD students (6 of them already defended) and welcomed four post-doctoral researchers. The team will also be soon reinforced by the recruitment of an additional permanent researcher with strong complementary expertise in NMR and dedicated funding (ERC starting grant). The Team has a broad international network of collaborators and had some invitations to international meetings in Europe (European Magnetic Resonance Meeting EUROMAR, Experimental Nuclear Magnetic Resonance Conference ENC, International Society for Magnetic Resonance in Medicine ISMRM, European Society for Magnetic Resonance in Medicine and Biology ESMRMB). Team members participated in the organization of national and international congresses in Europe (SFRMBM, Lorentz Workshop, 2 ESMRMB) and hosted two advanced foreign scientists from Cardiff (UK) and Sungkyunkwan (South Korea). All PhD students participate in national and international congresses. Over the period 2018-2023, the team published a total of 16 original and 5 review articles in excellent international [UMO1] journals of the discipline (e.g. Neuroimage, J Magnetic Resonance, Magnetic resonance in Medicine, NMR in Biomedicine), including 12 in leading positions and 6 involving PhD students. Team 4's responsibility for the platforms constituting the 7T and 11.7T MRI scanners ensures the equipment maintenance and needed expertise and has provided the grounds for many fruitful collaborations in the NeurATRIS et PASREL frameworks. It is commendable that the research activities estimated at 25% are delivering competitive funding, innovation and publications going far beyond the attributed activity percentage. The three main topics - diffusion-based spectroscopy, oxygen17 MRI and CEST MRI have been highly visible with several publications (n=28) in middle-tier specialised journals like MRM, Neuroimage, J Mag Res, Metabolites and HMG. The links to industry are strong (e.g. Servier) through the technological platforms and with TheraSonic - on the topic of blood-brain barrier modulation using focused ultrasound. The societal contributions include the work on a popularisation video on CEST MRI aimed at the general public. The team also presented a webinar organised by the European Infrastructure for Translational Medicine (EATRIS). Team 4 participated at the Open Days at the Fontenay-aux-Roses site, at the 'Women and Science' Forum (Lycée Buffon, December 2021) and at the 9th edition of the 'Scientifique toi aussi' science careers forum (CEA-FAR, January 2020). The high level of recognition in the scientific community is evident from the participation in the organising committee and scientific committee of the annual congress of the Société Française de Résonance Magnetic Resonance in Biology and Medicine SFRMBM (Paris, 2023), the co-organisation of a Lorentz Workshop on spectroscopy (Leiden, 2021) and the co-organisation of two ESMRMB 'Lecture on MR' sessions on diffusion spectroscopy (Paris, 2018; online, 2021).

Weaknesses and risks linked to the context

Overall, the team has few weaknesses. However, the team had few interactions with the academic world, and with the socio-economic world, apart from services with manufacturers (Servier) as part of "platform", and a collaboration with the startup TheraSonic. During the period, the team had limited interactions with the society but also with the clinics. Research therefore remains very fundamental in a field, neurodegenerative diseases, where both the need for therapeutic development is major and society's expectation of information is imperative. The team leader has-been nominated the director of the institute and will co-director of the structure for the next period, which may impact his availability to conduct his research

Analysis of the team's trajectory

This team started with 3 permanent researchers and responsibility for an imaging platform in January 2020. The team's research projects are based on a complementarity between aspects of cellular structure observed by magnetic resonance spectroscopy and energy metabolism (glucose, oxygen, lactate). It interacts within the unit with teams 3 and 6 for an access to non-human primates and complementary techniques. The remarkable success in obtaining European and national resources ensures the recruitment of future PhDs and post-docs, thus providing long-term visibility. In addition, a fourth permanent researcher will soon join the team.

Team's 4 coordinator role in the ERC Consolidator LactaDiff, ANR JCJC nrjCEST, the synImaging project funded by the Fondation de France and partnership in the ANR PRC projects: TreatPolyQ, ANR Brainfuel and ANR MetaTune have ensured a stable basis for a positive trajectory and sufficient knowhow and funding for the next evaluation period. The efficient use of two ultra-high fled 7T and 11.7T MRI scanners on the other side provides the high-end technological platform for continuation of the innovative research performed by the team.

RECOMMENDATIONS TO THE TEAM

The team's activity aimed at the cultural, economic and social world need to be improved as well as the link with the academic world in its immediate environment (teaching duties, Master's internships).

Even if the clinical world is not immediately accessible, given the location of the laboratory, the committee recommends discussing within the unit/team how to better develop translational aspects linked to the technological innovations for the benefit of patients with neurodegenerative disorders.

The team leader is also the future co-director of the unit. Care must be taken to ensure that he maintains the high-quality research dynamics of the team.

Team 5: Multimodal imaging

Name of the supervisor: Mr Marc Dhenain

THEMES OF THE TEAM

The Multimodal imaging Team (team 5) focuses on the characterisation of the biological mechanisms, in particular the prion hypothesis, involved in the development of Alzheimer's disease and the development of innovative imaging tools for monitoring brain pathology with a focus on 3D microscopic imaging methods based on high-performance computing (HPC) algorithms and resting-state fMRI for network characterisation.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

There were no specific recommendations for team 5 in the previous evaluation besides the common ones referring to the role of technical staff in the research activities of LMN.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2023

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**7**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	0
Doctorants	2
Sous-total personnels non permanents en activité	**2**
Total personnels	**9**

EVALUATION

Overall assessment of the team

Team's 5 overall **excellent to outstanding** evaluation is supported by an excellent organisation that contributed to achieving an excellent to outstanding attractiveness and outstanding scientific productivity. The team has to be commended for its outstanding work towards the society.

Strengths and possibilities linked to the context

During the period 2018 - 2023, Team 5 brought breakthrough evidence that amyloid and tau proteinopathies are transmissible and can induce neurodegeneration (Gary et al., 2019; Lam et al., 2021). The team has developed unique technologies and algorithms to perform neural network analysis that allow investigating the propagation of proteinopathies (Celestine, 2020). In addition, Team 5 has developed cutting-edge imaging tools (machine learning and deep learning segmentation of neuronal cells) for monitoring brain pathology (You et al. 2021 & 2022; Wu et al. 2022.). One of the major strengths of team's 5 research concept that supports its excellent to outstanding evaluation is the translational aspect building on the prion hypothesis of misfolded protein propagation in neurodegenerative diseases. The implementation of this concept in the murine microcebes aligns well with the inherent dependency between ageing and neurodegeneration.

Methodologically, the combination between the development of 3D microscope imaging techniques with high-performance computing and resting state functional MRI provides an edge that ensures both the excellent to outstanding attractiveness and the outstanding scientific productivity. The outstanding scientific productivity is characterised by the publication of 61 articles (60% from inter-team collaborations), including 28 as first or last author (43% published by a PhD student). The excellent to outstanding attractiveness is also supported by the strong involvement in student training and teaching (organization DIU translational neurology, doctoral school - steering committee and M1, M2, PhD) with 11 PhD candidates trained during the evaluation period. The high level of research activity is supported by competitive funding (Alzheimer's disease associations, 3 ANR) and industrial funding for a total of €1233k, including €738k over the evaluation period. Similarly, the team's recognition in the scientific community is evident from more than 30 invitations to national and international forums including the Club Recherche Alzheimer: Compréhension - Thérapie - Ile-de-France (58 seminars since 2016). The PIs are members of key societies and governing bodies at the national and international level, most notably the medical (ANM) and veterinary (AVF) French academies, the vice-presidency of the AVF research committee (2017-2020), membership of the AVF board of directors (2018-2021), leadership of the AVF COVID unit (2020-2022), the ANM veterinary section (2022-now), membership of the inter-academy group (ANM, AVF, pharmacy, science) on the use of animals for scientific purposes and membership of the FC3R steering committee. Another PI is a member of the Scientific Council of France Alzheimer, Vice-Chairman of the Scientific Council of France Alzheimer, Board of Directors of the Alzheimer Foundation, Member of the Scientific Council of the ANR (CE18). The team's outstanding contributions to society are visible through the outreach efforts to scientific and non-scientific audiences (Press articles: > 80, TV/Radio: 10, France Alz/Vaincre Alz: Patient days).

Weaknesses and risks linked to the context

Despite the team's closure and the departure of 3 researchers, there are no major weaknesses or risks for team's 5 trajectory. Over the next period, however, the team will need to remain vigilant about the gender ratio among scientists and need to attract more early career scientists (only 2 post-doc 2018-2023).

Analysis of the team's trajectory

Team 5 has an upward trajectory excelling at the evaluation topics of scientific productivity and contribution to society. The adopted scientific concept about the prion-like behaviour of misfiled proteins at the core of Alzheimer's disease has been fruitful in the translational implementation at the unit. The unique 3D miceroscopical imaging, embedded in solid high-performance computing framework and strong collaborations with leaders in the field proved the success of the team in terms of attractiveness through the acquired competitive funding and milestone publications.

Now, the unit will be dissolved with only a few researchers remaining at MIRcen's Laboratoy of Multiscale Brain Image Analysis, the CEA – Service com, or the laboratory of modelling and biotherapies for proteinopathies.

RECOMMENDATIONS TO THE TEAM

Given the fact that the team's CNRS PIs are currently in the transitional phase with the majority of scientists moving to Neuro-Bicêtre, there is a clear need to ensure the MirCen support for the microbus stalls and the access to essential imaging equipment. In the same context, initially, there will be the possibility of losing the team's thematic coherence, which should be mitigated by new collaborations at the respective receiving sides.

Team 6: Preclinical and clinical therapeutics

Name of the supervisors: Mr Philippe Hantraye & Ms Romina Aron Badin

THEMES OF THE TEAM

The preclinical and clinical therapeutics team (team 6) focuses on the development of preclinical models to test the efficacy, biodistribution and safety of therapeutic approaches in neurodegenerative diseases. In addition, team 6 is focused on the discovery of specific and selective biomarkers to better diagnose and monitor patients with neurodegenerative diseases.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

There were no specific recommendations for team 6 in the previous evaluation besides the common ones referring to the role of technical staff in the research activities of LMN.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2023

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	3
Chargés de recherche et assimilés	3
Personnels d'appui à la recherche	15
Sous-total personnels permanents en activité	**21**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	0
Doctorants	2
Sous-total personnels non permanents en activité	**2**
Total personnels	**23**

EVALUATION

Overall assessment of the team

The overall evaluation of team 6 is **excellent to outstanding** - motivated by an outstanding organisation and attractiveness, most importantly carried by the leadership of the NeurATRIS programme securing the purchase of a cyclotron and a radio-chemistry laboratory in 2023. The scientific productivity is accordingly evaluated as excellent to outstanding, the contributions to society which is also excellent.

Strengths and possibilities linked to the context

Team 6's achievements in the past period are excellent to outstanding. The team, consisting of well-balanced ratio between researchers (n=8), engineers (n=8) and technicians (n=8.5) has brought unique insights with animal models of neurodegeneration that ensured competitive and industrial funding. Team 6 research findings and the creation of novel biomarkers for alpha-synucleinopathies provided the backbone for coordinating the NeurATRIS funded cyclotron and radiochemistry laboratory, and paved the way for genetic therapy in Parkinson's disease that is now in the clinical testing in the USA. Team 6 is outstandingly attractive through its translational work from bench to bedside, through significant competitive EU funding and leadership in international research consortia ((Repair-HD (602245); BrainMatTrain (676408); EATRIS-Plus (871096)), EATRIS-

CONNECT (INFRA-DEV-03-2023); €291k), and national initiatives (NeurATRIS; €12.5Mio) and industry contracts totalling €18.6Mio for the evaluation period. Its attractiveness stems from a proactive policy supporting early career researchers and promoting individuals. Team 6 is maintaining a unique technological platform that allowed for an excellent to outstanding scientific productivity (n=52 articles, n = 19 with first and last authorship; hereunder 15% doctoral students with first and last authorship). The excellence of team 6 attracted seven Masters students, six PhD students (including 1 from abroad), 1 engineer and 1 post-doc (from abroad,) with an overall equal gender balance at all hierarchical levels. The team's PIs are positioned at important research committees including seats on the steering committee of the international consortium SC4HD and the EHDN Advanced Therapies Working Group, the presidency of NECTAR - the European transplantation and regenerative therapies for neurodegenerative diseases and invitations to the ESMI courses on PET imaging and modelling and the EATRIS 'imaging & tracers' steering committee.

Weaknesses and risks linked to the context

Team 6 is in an excellent position to carry on with the outstanding work programme followed in the last evaluation period. There is solid funding that goes far beyond the institutional support, which is building based on the NeurATRIS programme.

The only potential risk for team 6 pertaining also to the new structure of the future CEA unit is the theoretical reduction in scientific projects for the benefit of industrial contracts. The fine balance, which is needed to maintain the financial stability of research infrastructure should not prevail and overcome the scientific ambitions of the team.

Analysis of the team's trajectory

The team's 6 trajectory is an upward trajectory. The team is organised in most efficient way to perform outstanding research using unique technologies. The team's research strategy has brought the leadership of the NeurATRIS programme, which beyond the solid funding provided a visibility beyond the national borders and beyond the current funding period. Team 6 staff is perfectly situated to maintain both equipment and scientific projects throughout the transition times seeing many LMN researchers leave for their new CNRS home institutions. The established dual strategy combining a novel and patent-seeking characterisation of alpha-synucleins with industry projects secured a niche in the domain bringing not only top-tier projects (ANR, GAO France Parkinson, contract with AClmmune), but also forward looking vision with potential clinical applications currently (https://clinicaltrials.gov/study/NCT03720418) and in the next funding period. Similarly, the highly innovative tools developped by the team in collaboration with PTCTherapeutics ensure a leadership in this market niche with potential to grow both academically and financially. The involvement in several EU projects, on the other side, provided the high visibility of the team in the EU research ecosystem that will continue carrying fruits for the future.

RECOMMENDATIONS TO THE TEAM

Though impressed by the achievements of team 6, the evaluation committee recommends a careful study of the strengths and weaknesses of the newly formed CEA unit that should lead to a shared vision where team 6 should prove to be a reliable backbone - both in terms of stable funding and in terms of scientific direction. Here, the fine balance between contractual "services" for industrial partners and investment in scientific new land should be maintained.

Team 6 should be open to the clearly needed Inserm affiliation and the opening of new avenues for affiliation with the Faculty of Medicine and/or Faculty of Pharmacology at the University Paris-Saclay.

CONDUCT OF THE INTERVIEWS

Date

Start: 10 décembre 2024 à 09h00

End: 10 décembre 2024 à 18h00

Interview conducted: on-site

INTERVIEW SCHEDULE

RDV : 8h00 : accueil CEA

8:20-8:30 Présentation du processus d'évaluation par le conseiller Hcéres et du comité d'experts

Salle de conférence R+2 (201)

8:30-9h15 Présentation de l'Unité et de ses thématiques de recherche (réunions publiques) par les directeurs d'Unité : Drs G. BONVENTO, J. VALETTE et R. ARON BADIN [30 min de présentation / 15 min de discussion)]. Salle de conférence R+2 (201)

9:15-10h15 Présentation des équipes de recherche (réunions publiques). Salle de conférence R+2 (201)

9h15-9h45 : Equipe « Protein misfolding and aggregation » par le Dr R. MELKI [15 min de présentation [15 min de présentation (10 min bilan + 5 min projet) / 15 min de discussion)]

9h45-10h15 : Equipe « Cell-cell interactions » par les Drs A. BEMELMANS et A. PERRIER [15 min de présentation (10 min bilan + 5 min projet) / 15 min de discussion)]

10:15-10:45 Pause

10:45-12h45 Présentation des équipes de recherche : suite (réunions publiques). Salle de conférence R+2 (201)

10h45-11h15 : Equipe « Molecular complexity of reactive astrocytes » par le Dr C. ESCARTIN [15 min de présentation (10 min bilan + 5 min projet) / 15 min de discussion)]

11h15-11h45 : Equipe « Advanced magnetic resonance to probe brain cell alterations in vivo » par le Dr J. VALETTE [15 min de présentation (10 min bilan + 5 min projet) / 15 min de discussion)]

11h45-12h15 : Equipe « Multimodal imaging » par le Dr M. DHENAIN [15 min de présentation (10 min bilan + 5 min projet) / 15 min de discussion)]

12h15-12h45 : Equipe « Preclinical and clinical therapeutics » par les Drs P. HANTRAYE et R. ARON BADIN [15 min de présentation (10 min bilan + 5 min projet) / 15 min de discussion)]

12:45-13:30 Pause déjeuner

13:30-15h30 Discussions à huis clos entre le comité et les différentes catégories de personnels. Salle de conférence R+2 (201)

- 13:30-14:00 Discussion avec ingénieurs, techniciens, personnels administratifs.
- 14:00-14:30 Discussion avec les étudiants en thèse et les post-docs.
- 14:30-15:00 Discussion avec les scientifiques (sans le DU et les chefs d'équipes).

15:00-15:30 Discussion avec les chefs d'équipes (sans le DU). Salle de conférence R+2 (201)

15:30-16:00 Huis Clos du comité pour préparer les échanges/questions avec DU et tutelles. Salle de réunion R+2 (213)

16:00-16:30 Discussion avec le DU. Salle de réunion R+2 (213)

16:30-17:00 pause

17:00-17:30 Discussion avec les représentants des organismes de gestion/tutelles. Salle de conférence R+2 (201)

17:30-18:00 Huis Clos du comité en présence de CS Hcéres en vue de la préparation du rapport. Salle de réunion R+2 (213)

18:00 Fin de la visite

GENERAL OBSERVATIONS OF THE SUPERVISORS

The institution responsible for submitting the application, which is also responsible for coordinating the response on behalf of all the research unit's supervisors, did not submit any general observations.

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