

EVALUATION REPORT ON THE UNIT:

MMDN - Mécanismes Moléculaires dans les
Démences Neurodégénératives

UNDER THE SUPERVISION OF INSTITUTIONS AND RESEARCH BODIES:

Université de Montpellier - UM

École pratique des hautes études - EPHE-PSL

Institut national de la santé et de la recherche
médicale - Inserm

EVALUATION CAMPAIGN 2025-2026
GROUP A



On behalf of the committee of experts:

Nathalie Sans, Chairperson of the committee

For Hcéres:

Coralie Chevallier, President

In accordance with articles R. 114-15 and R. 114-10 8° of the Research Code, evaluation reports drawn up by the committees of experts are signed by the chairpersons of these committees and countersigned by the president of Hcéres.

To facilitate the reading of the document, the terms used in this report to designate functions, occupations or responsibilities (expert, researcher, teacher researcher, professor, lecturer, engineer, technician, director, doctoral student, etc.) are generic and gender neutral.

This report is the outcome of an evaluation by a committee of experts the composition of which is specified below. The assessments it contains are an expression of the independent and collegial deliberation of the committee. The data within it are the certified accurate data extracted from the application forms submitted by the supervising bodies on behalf of the unit.

This version of the report is public under Article R. 114-23 of the Research Code. Sections of the report considered confidential, and responses to points of attention from supervisors are not included in it.

MEMBERS OF THE COMMITTEE OF EXPERTS

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Experts:

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Mr Pierre-Olivier Fernagut, DR, CNRS, Poitiers (representative of CSS Inserm)

Mr Nicolas Stadler, IR, Inserm, Paris (supporting personnel)

Mr Rachid Soulimani, PR, Université de Lorraine, Metz (representative of CNU)

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Ms Claudie Doums, doyenne de la section "Sciences de la vie et de la terre", École Pratique des Hautes Études

UNIT CHARACTERISATION

- Name: Mécanismes Moléculaires dans les Démences Neurodégénératives
- Acronym: MMDN
- Label and number: Inserm UMR_S1198
- Number of teams: 4
- Composition of the executive team: Mr Tangui Maurice (director) and Ms Nadine Mestre-Francés (deputy-director)

SCIENTIFIC PANELS OF THE UNIT

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

THEMES OF THE UNIT

The main research focus of the MMDN is fundamental and translational research on ageing and neurodegenerative disorders, with a particular emphasis on Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), Wolfram syndrome, and spinal cord injury. MMDN is an interdisciplinary laboratory with approaches ranging from cell culture, cellular and molecular biology, development of preclinical models in several species (drosophila, zebrafish, mouse, microcebus murinus) to epidemiology and societal research. Thanks to the combination of these different levels of investigation, the majority of the projects carried out by MMDN are in a translational framework.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The laboratory Molecular Mechanisms in Neurodegenerative Dementia (MMDN, Inserm UMR_S1198) is a research unit jointly administered by Inserm, the University of Montpellier and the École Pratique des Hautes Études (EPHE-PSL, 7 assistant and equivalent professors). The unit was created in 2005 by Jean-Michel Verdier and is currently directed by Tangui Maurice (CNRS research director) since 2018, following the election of Jean-Michel Verdier as president of EPHE. The research unit is located in the main campus of the Faculty of sciences (campus Triolet), in the historical building of the Biology & Health scientific department of the university (DSBS). The DSBS is composed of 28 research units and one technological platform. The MMDN laboratory is currently organized as a monothematic laboratory with four independent research groups. For the next mandate, Tanguy Maurice proposes a two-team project and the appointment of Benjamin Delprat as the future unit director.

UNIT RESEARCH ENVIRONMENT

MMDN is a component of the pole biology & health of the university of Montpellier. The laboratory is involved in several local networks. It is a founding member of the multi-platforms service unit BIOCAMPUS (UAR 3426 CNRS - US 09 Inserm - UM) and hosts several components of the platforms of BIOCAMPUS (CECEMA, part of the RAM platform, and part of the ZEFIX platform). MMDN has strong interactions with the university hospital (CHU) of Montpellier, notably through clinicians associated with groups 2 and 3. Group 4 of MMDN (Environmental impact in Alzheimer's disease) is a member of the labex LIPSTIC (lipoprotein and health). MMDN is also highly involved in technological transfer and valorization and as such interacts closely with the SATT AXLR and the "direction de l'innovation et des partenariats" (DIPA) at the University of Montpellier. MMDN is a founding member of the transdisciplinary Institute for the study of ageing (ITEV, "EPHE-PSL Institute"), that brings together research, education to strengthen the link between science and society. Several members of the unit are in the executive team and ITEV is currently headed by a member of MMDN.

MMDN is a founding member of the center of excellence for neurodegenerative disorders (CoEN) and has strong interactions and collaborations with other research units in neurosciences in Montpellier (INM and IGF). Together with IGF and INM, MMDN contributed to federation of neuroscience laboratories with the creation of "Montpellier Neurosciences". MMDN is a member of the I-Site Montpellier university of excellence (previously MUSE) and was also involved in creation of the center of excellence on autism and neurodevelopmental disorders (CoEAND).

UNIT WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	4
Maitres de conférences et assimilés	7
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	3
Personnels d'appui à la recherche	11
Sous-total personnels permanents en activité	27
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels non permanents d'appui à la recherche	7
Post-doctorants	4
Doctorants	6
Sous-total personnels non permanents en activité	19
Total personnels	46

BREAKDOWN OF THE UNIT'S PERMANENT STAFF BY EMPLOYER: IN PHYSICAL PEOPLE AS OF 31/12/2024. NON-SUPERVISING EMPLOYERS ARE GROUPED ON THE HEADING "OTHERS".

Nom de l'employeur	EC	C	PAR
U Montpellier	2	0	3
Inserm	0	3	3
EPHE-PSL	7	0	5
Autres	2	2	0
Total personnels	11	5	11

GLOBAL ASSESSMENT

MMDN is an excellent unit dedicated to integrated and interdisciplinary neuroscience research from the cellular and molecular mechanisms involved in neurodegenerative diseases to the pathological processes related to these neurodegenerative pathologies, bringing together multidisciplinary teams whose expertise is recognized nationally and internationally. Its work aims to establish a translational continuum between basic research and clinical application. The institute stands out for its integrated approach on *Microcebus murinus* leveraging the specie long lifespan to conduct longitudinal studies on physiological aging and neuropathology. The MMDN stands out for the quality and originality of its research with a particularly highly competitive and outstanding group on the cellular determinants of neuroprotection (Team 2). The work carried out at the MMDN, particularly on the mechanisms of neurodegeneration, early biomarkers, and innovative therapeutic strategies, give the institute an excellent reputation in the national and international research ecosystem on these topics. In term of organization, the unit is organized with a governance structure that encourages participation by all members, from researchers to technical staff. Strategically, the MMDN has chosen to strengthen its infrastructure to support ambitious projects, notably by modernizing its technological platforms and developing innovative tools for studying molecular mechanisms. A particular attention is being paid to accelerating the transfer of results to clinics, with enhanced collaborations with in house or local biotech companies. The MMDN is also involved in flagship projects, such as the development of early biomarkers and targeted therapies for Wolfram syndrome, in collaboration with industrial partners. The institute has also initiated programs aimed at optimizing the use of its platforms as vectors for development for local teams and external partners. The MMDN plays an active role in consolidating a dynamic research network in Montpellier, strengthening synergies between academic and industrial players. The unit is a member of MUSE (Montpellier University of Excellence) and participates in

numerous scientific networks: BIOCAMPUS, CALM, CoEN, CoEAND. It maintains international collaborations (NIDA, Ferrara, Liège, Taipei, Mayo Clinic) and coordinates the Cost Action SIGMA1 Europe (26 countries). Links with Montpellier University Hospital promote clinical translation. Indeed, all teams are involved in translational projects. As a result, the MMDN is active in promoting innovation. It holds 8 patents and 2 others pending. The unit has partnerships with SITERA Pharmaceuticals, a start-up recently created by MMDN members), REST Therapeutics and RD Nephrology. The MMDN regularly organizes or hosts a wide range of internal, local, and international events—an essential component in fostering the professional development and scientific growth of students and postdoctoral researchers. The dissemination of knowledge, both to the scientific community and the general public, is a priority, as illustrated by outreach activities and collaborations with patient associations.

Overall, it appears that the MMDN is among the leading centers for research on neurodegenerative disorders in France, effectively combining fundamental research, translational approaches, and clinical engagement. The institute's ongoing efforts to reorganize its structure, strengthen collaborations between members, and facilitate the transfer of innovations to clinics have established it as a significant player in the field and have consolidated its international competitiveness. The emerging opportunities—particularly in innovative therapies and biomarker discovery—hold considerable promise and would benefit from continued support.

DETAILS OF THE EVALUATION OF THE UNIT

A - CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The MMDN has clearly considered and acted on the recommendations outlined in the previous Hcéres report, implementing substantial improvements across nearly all areas. Notably, the unit has elevated the quality of its publications, securing placements in high-impact journals, and established robust internal review processes to sustain this advancement. It has also enhanced the validation and translational relevance of its animal models, while expanding collaborations within the perimeter of the University of Montpellier and clinical partners. Additionally, the MMDN has significantly increased its research funding and strengthened industrial engagement.

Regarding its organization, the unit has begun a transition toward a restructuration from its historical axes of four groups into two main complementary teams, fostering greater internal synergy and coherence. Initiatives in mentoring, ethics, and data sharing have been reinforced through formal policies and regular activities, cultivating a collaborative and supportive work environment.

While challenges persist, particularly in recruiting and retaining PhD students and fully implementing electronic data management tools, the MMDN's overall progress reflects a proactive response to the Hcéres recommendations. This has resulted in measurable advancements in scientific quality, structural organization, and broader impact and missions toward the development of new diagnostic and therapeutic strategies for neurodegenerative diseases.

B - EVALUATION AREAS

EVALUATION AREA 1: THE UNIT'S SCIENTIFIC OBJECTIVES, ORGANIZATION AND RESOURCES

Assessment of the unit's scientific objectives, organization and resources

The unit's scientific objectives, scientific organization and resources are **excellent to outstanding**. The unit's activities extend from fundamental neurosciences to the development of new diagnostic and therapeutic strategies for neurodegenerative diseases and align well with the local neuroscience strategies. The unit has an original positioning on diseases (ex: Wolfram Syndrome) and pathophysiological mechanisms (ex: Sigma 1 receptor, Reg1-alpha). Through clearly defined and relevant scientific objectives, the MMDN has made significant contributions to understanding the early mechanisms of neurodegenerative diseases by developing innovative models for diagnostics and therapy. Its multimodal approach—integrating cellular, rodent, fly, zebrafish and primate models—seems quite effective and original to bridge the gap between fundamental and preclinical research on human pathologies. This was achieved thanks to efficient organization and management policies. MMDN has been able to achieve its scientific goals by leveraging appropriate human and financial resources. The unit will need to ensure that an adequate balance between basic science and valorization efforts will be maintained. The implementation of data storage and protection policies is also a priority for the next mandate.

Context-related strengths and opportunities for the four references above

The MMDN has defined ambitious and relevant scientific objectives that are perfectly aligned with the challenges in its research field. These objectives have been developed to respond to current and emerging challenges in neuroscience and translational medicine, while pursuing a proactive approach to translational and clinical projects. During the evaluation period, the unit has published several relevant high-quality publications (Nature Comm, Science Advances, Sci Reports, etc.). The MMDN's group' objectives have been designed to align with the strategic priorities of its supervisory bodies, in particular the EPHE, Inserm and its academic and clinical partners. The unit has identified and strengthened its collaborations with major local players, both at the academic level and in industry. These partnerships not only enrich scientific projects, but also facilitate the exploitation of results, particularly through development of startups, clinical and technological applications. The MMDN's research policy is structured to ensure an integrated approach, ranging from fundamental research to clinical translation. The unit places particular emphasis on the exploitation of results, whether through publications in a wide range of journals including high-quality journals, patent filings, or industrial collaborations. This strategy ensures the optimal dissemination of results. The MMDN's internal organization into 4 groups has been redesigned to promote synergy between researchers into the groups and optimize the implementation of its strategy. The restructuring into two complementary teams will improve project coordination, and strengthen scientific consistency. In summary, MMDN has developed a clear scientific strategy, an appropriate organizational structure, and a network of strong partnerships, enabling it to meet the committee's expectations while pursuing its ambition toward understanding pathological processes related to neurodegenerative pathologies. The MMDN has human, technical, and financial resources that are suited to its scientific ambitions and its position within the Montpellier and national research ecosystem. The unit, while small in size, has been successful in attracting or recruiting several researchers from Inserm, CNRS, UM and EPHE. Several research support staff and young researchers also joined the lab during the period. The MMDN's objectives in term of grant funding is excellent and diversified (ANR, Europe, industrial partnerships, clinical contracts) to support ambitious projects, from basic research to translation. The financial resources through small or medium funds and competitive national and international funding including foundation or associations representing 88% of obtained funds, are outstanding showing a significant increase of 21% compared to the previous period. This includes 1 international private grant (Biogen), 2 European contracts (Horizon Europe, Action COST), 5 ANR grants, 3 of which are supported by the teams, 21 contracts funded by the PIA and 32 grants from charities and foundations (FRM, Fondation France Alzheimer, AFM, Retina France, FPA, Fondation France Wolfram, Fondation Verticale, etc.). An important income source also comes from partnerships with the socio-economic and cultural environment (ex: SATT AXLR, SITERA, ANAVEX, REST Therapeutics, Campus France) and from contracts with local authorities (ex: Occitanie region, EPHE, Montpellier University Hospital). The unit has been able to take advantage of its rich environment regarding cutting-edge technological platforms with its participation to the BIOCAMBUS research support unit (imaging, animal models, bioinformatics tools, etc.). The MMDN has its own zebrafish facility that integrate all aspects of research and is in charge of the non-human primate facility. The MMDN has implemented a proactive policy of sharing resources and data, in line with the principles of open science and has a culture of collaboration, illustrated by multi-partner projects and co-publications with national and international teams. The unit has strengthened its integration and skills development policy with a structured welcome program for new members (doctoral students, post-doctoral researchers, researchers), including mentoring and targeted training. Career support initiatives, such as workshops on research promotion, project writing, or preparation for competitive examinations (e.g. CNU qualification) is also implemented in the lab. A focus on work-life balance, with initiatives to promote gender equality and professional parity or quality of life at work are among the notable actions. Following Inserm policy, the MMDN unit has a referent for gender equality and professional parity since 2022. The unit also has a reglementary position for a health and safety prevention assistant, and has established a Quality of Life at Work unit and appointed a responsible for sustainable development with an Eco-labo working group. The unit strictly adheres to institutional guidelines and regulations in its approach to preventing sexual harassment, workplace bullying, and discrimination. Similarly, its policies for intellectual property protection and IT security are fully aligned with the established frameworks and standards.

Context-related weaknesses and risks for the four references above

1/ The recent restructuring into two complementary teams has clarified responsibilities, and should strengthen scientific goals. It will be necessary to setup regular monitoring mechanisms, such as internal discussions and presentations of projects to ensure that the objectives set are achieved in an efficient and collaborative manner. There is always a risk of going back to former projects and inefficient collaboration or misalignment with strategic objectives.

2/ A potential challenge for the unit will lie in striking balance between the management of startups and the pursuit of its own core scientific priorities. While the current leadership has successfully navigated this transition, the new direction must ensure long-term sustainability. Overemphasis on entrepreneurial activities could divert focus from academic priorities, and private-sector partnerships may introduce ethical tensions or conflicts with the unit's fundamental research goals.

3/ A potential vulnerability lies in maintaining equilibrium between laboratory research and the integration of shared facilities. There is a need to better formalize ITA/ITRF roles and implications in the UA.

Societal debates—particularly regarding non-human primate research and neuroscience ethics—could constrain project feasibility.

4/ The unit's practices comply with the rules and guidelines set by its supervisory bodies in terms of human resources management, safety or compliance for intellectual property. Data storage and protection could be considered as a risk for the unit.

The lack of governance strategies sharing at the level of the site could potentially isolate the unit and limit opportunities for sustaining and strengthening key technical positions and for synergy or even reduce visibility within the broader research ecosystem in Montpellier.

EVALUATION AREA 2: THE UNIT'S SCIENTIFIC RESULTS, IMPACT AND ATTRACTIVENESS

Assessment of the unit's scientific results, impact and attractiveness

In the Montpellier dynamic scientific hub, the MMDN is undoubtedly one of France's recognized neuroscience research centers dedicated to research on the biology of aging, neurodegenerative and other rare disorders. It brings together renowned experts in various fields, with a particular focus on neurodegenerative diseases but also some rare pathologies. The institute's scientific output is **excellent to outstanding**. The quality and originality of the work carried out and the remarkable visibility of its teams are major assets, reinforcing the attractiveness and reputation for excellence of this unit. It is, however, noteworthy that the unit welcomed a low number of foreign researchers including visiting scholars and doctoral students or postdoctoral early career researchers.

Context-related strengths and opportunities for the four references above

The MMDN is widely recognized for its scientific achievements, particularly in unraveling the molecular mechanisms underlying rare and neurodegenerative diseases such as Wolfram, Alzheimer's, ALS's, Parkinson's, and tauopathies. The unit is also recognized for its historical research using mouse lemurs as a model. The unit's high-quality research, published in recognized journals (Neurobiology of Aging, Scientific Reports, Brain Behavior), underscores its relevance and impact in the field and attests to the quality of its research. The use of innovative animal models—including lemurs, fruit flies, and zebrafish—alongside advanced techniques like viral gene transfer, imaging, and behavioral analyses, further solidifies its reputation both nationally and internationally. The lab has shown its ability to expand translational research to accelerate the transition from basic research to clinical applications, such as biomarkers or therapies for Alzheimer's. Moreover, the unit capitalizes on scientific achievements to create start-ups (SITERA) focused on diagnostic tools or neuroprotective therapies. The MMDN's scientific output is excellent to outstanding in light of its size, producing highly original and specialized research articles. Over the reporting period, the unit published 123 original articles, 23 reviews, and 24 clinical papers, reflecting its focused expertise and productivity. Around half of this production is signed by MMDN as first, last or corresponding author and one third are also signed by PhD students. Original articles are published both in leading specialist journals (ex: Alzheimer Research and Therapy, Redox Biology, Neuroendocrinology, Autophagy), as well as in high profile general interest journals (ex: Nature Communications, Science Translational Medicine, Science Advances). A key strength of the MMDN lies in its integrated and collaborative approach. The inclusion of clinicians within research teams enhances the translational value of its work, ensuring that fundamental discoveries are effectively linked to clinical applications. The institute's teams benefit from strong methodological complementarity, enabling seamless collaboration across molecular, systems, and behavioral neuroscience. This interdisciplinary synergy drives innovation and efficiency in multi-level investigations. Furthermore, the MMDN maintains extensive and productive collaborations with other research groups in Montpellier, as well as with national and international partners, amplifying its scientific reach and influence. The scientific output of the MMDN is both quantitatively sustained and qualitatively recognized. Publications targeting peer-reviewed journals with a high-quality production are consistent, reflecting the excellence of the work carried out. For example, studies on tauopathies, biomarkers such as REG-1alpha, and metabolic mechanisms in neurodegeneration are regularly published in specialized journals. Others studies on Wolfram syndrome or ALS target highly recognized journals. In most cases, the diversity of experimental models and interdisciplinary collaborations ensures robust and varied scientific output. Finally, most publications are in collaboration with national and international teams broaden the scope and impact of research findings. MMDN takes a leading role in fostering scientific collaboration and community engagement. Through its involvement in national and international research networks but also the organization of thematic workshops, the laboratory creates dynamic opportunities for knowledge exchange and shared resources, including biobanks and animal models. Beyond collaborative research, MMDN is deeply committed to mentoring the next generation of scientists, further strengthening its reputation and impact within the scientific community. During the past contract, the unit has trained 14 PhD students and 7 post-doctoral

fellows have. Eight PhD students and two post-doctoral fellows are currently trained in the unit. Regarding the influence of the unit, it is quite excellent with a large network of national and international collaborators. The Unit also welcomed visiting scientists (8 PHC Campus France, 2 DAAD and BabyFrance and 1 adelante2 exchange programs) highlighting its high level of attractiveness. In particular, the unit co-directed PhD thesis with Cuba, Georgia and Germany. Several members of the unit have received awards and/or distinctions (Knight of the National Order of Merit, thesis prize, Rotary Club/FRC prize) and have been invited to give lectures (>80) at international conferences (IBRO, European symposium on sigma-1, Japanese pharmacological society, etc.) and national conferences (NeuroFrance, Académie de Médecine, etc.). Finally, some members have participated in the organization of 32 symposiums/conferences/seminars (Winter Conference on Brain Research, USA; European Symposium on the Pathophysiology of Sigma 1 Receptor, Italy, Lithuania, etc.) and hold positions of responsibility within learned societies (Fondation Vaincre Alzheimer, Société de Neuroendocrinologie, Action COST, etc.). The MMDN seems to uphold high standards of scientific integrity and ethical responsibility in all its research activities. The team ensures both the reliability of findings and the transparency of processes. Committed to open science, MMDN actively promotes data sharing, provides access to its biobanks, and prioritizes publishing in open-access journals whenever feasible. Additionally, the laboratory strictly follows ethical guidelines for animal experimentation and clinical research, aligning its practices with societal expectations and fostering trust in its scientific contributions.

Context-related weaknesses and risks for the four references above

Regarding attractiveness, one can notice the low number of foreign postdoctoral researchers.

EVALUATION AREA 3: INCLUSION OF RESEARCH ACTIVITIES IN SOCIETY

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

The unit's research activities with and toward the society are excellent. The MMDN demonstrates a strong and multifaceted contribution to society, reflected in its active collaborations with industry, development of products with societal impact, and sustained commitment to public engagement and education.

Context-related strengths and opportunities for the three references above

Regarding interactions with the non-academic world, the unit stands out for its dynamic partnerships with private companies (STE SCHNEIDER ELECTRIC, STE BIOPROJET, STE ANAVEX LIFE SCIENCES) and technology transfer structures, resulting in tangible outcomes such as patents (8 patents and 2 more to come), creating start-ups transferring innovation generated in the laboratory (SITERA PHARMACEUTICALS), and 2 CIFRE industrial and 1 PhD program (e.g. RD Nephrology, Biogen). The company joined TTM factory, the SATT AXLR incubator, in december 2024 and applied for i-Lab funding in march 2025. These collaborations are recognized institutionally (Companies on Campus label, University of Montpellier, 2021 & 2023) and demonstrate MMDN's ability to transform fundamental research into innovation with clinical and economic potential. Such partnerships not only enhance the unit's visibility but also strengthen its capacity to attract competitive funding and foster employability for young researchers. MMDN's research output extends beyond academia through the creation of therapeutic innovations (new ligands), protected by patents and developed into preclinical and clinical programs, thereby contributing to healthcare innovation and regional economic growth. Furthermore, its involvement in continuing education (EPHE, PSL) and participatory research initiatives (ITEV, REIACTIS, Design citoyen) demonstrates a broader societal relevance, linking neuroscience with public health, autonomy, and aging. These actions position MMDN as a cross-disciplinary actor bridging biomedical research, social science, and policy innovation. The unit shows a deep commitment to science communication, with researchers frequently participating in public events (Fête de la Science, Semaine du Cerveau, Agora des Savoirs, A Pint of Science) and media outreach (France Culture, Le Monde, Science & Vie). The active involvement of staff and students in school outreach programs (Déclics, Apprentis Chercheurs) and public debates on sensitive topics (vivisection, aging, neurodegeneration) reflects a strong culture of civic engagement and responsibility. MMDN effectively contributes to raising scientific literacy and stimulating public dialogue on contemporary biomedical issues. Finally, The SIGMA1 EUROPE COST Action (CA23156), launched in 2024, represents a major driver in strengthening and structuring the European community working on sigma-1 receptors. Bringing together 26 partner countries and 300 members, it fosters coordinated progress through five working groups covering innovative chemistry, physiopathology, pharmacology standardization, translational requirements and broad dissemination. Beyond its scientific aims, the COST Action plays a crucial role in developing dynamic networks of local, national and international collaborations, an essential condition for ambitious funding strategies and high-impact publications.

Context-related weaknesses and risks for the three references above

Despite these strengths, a few potential weaknesses and risks can be identified.

1/ Sustaining multiple start-ups and collaborative agreements may require significant administrative and managerial resources, posing a challenge to balance scientific productivity and valorization efforts.

2/ While public engagement is rich and diverse, the impact evaluation of these outreach activities (e.g. on societal perception or policy influence) remains limited. A more structured strategy could help assess and enhance their effectiveness.

3/ Finally, the unit's growing involvement in societal and interdisciplinary initiatives implies a need for continued institutional support to maintain the momentum and ensure long-term sustainability of these actions.

ANALYSIS OF THE UNIT'S TRAJECTORY

For the next contract, MMDN proposes a restructuration from its historical axes of four groups into two main complementary teams, fostering greater internal synergy and coherence: Cellular DYNAmics and MOlecular specificity of neurodegeneration (DynaMo) and Pharmacological Approaches to Oxidative stress and Neuroinflammation (PAON). Consequently, rather than increasing the number of teams, the institute is focusing on stabilizing and reorganizing its driving research forces, while consolidating its partnerships with clinical and industrial players. This restructuring appears coherent given the size of the unit and scientific expertise of the different groups, and should optimize the use of both human and financial resources. It will also help the development of emerging project such as the one proposed on SPG7. Appropriate organization and management will be key to ensure the success of this new organization and to maintain a good equilibrium between core scientific objective responding to the major challenges currently facing neurodegenerative diseases and valorization activities.

The projects for the next contract are in line with the recognized expertise and previous achievements of the unit. They are centered around a restricted number of pathophysiological mechanisms (exposome, oxidative stress, inflammation) and targets (ex: sigma-1 receptor, Reg-1alpha) that will be investigated in several neurodegenerative disorders. Such transnosographic approach is appropriate given the workforce of the unit. MMDN will need to preserve its levels of funding (institutional, competitive project funding, and private) and recruitment strategy during the next contract in order to reach the proposed objectives and maintain it high scientific output. Given that recruiting new researchers is a long-term effort, an ambitious recruitment strategy at the level of the unit should be engaged immediately. It would be appropriate to begin implementing a clear research data management policy at the laboratory level, potentially through the use of an institutional data warehouse.

RECOMMENDATIONS TO THE UNIT

Given that the four team will reorganize into two new different teams for the next contract, recommendations are only given for the whole unit

RECOMMENDATIONS REGARDING THE EVALUATION AREA 1: SCIENTIFIC OBJECTIVES, ORGANIZATION AND RESOURCES OF THE UNIT

The unit is highly efficiently organized, enabling all staff members to actively participate in both research activities and the unit's daily life—though there is always room for improving internal communication and collaborations between the four groups could be optimized to strengthen cohesion and collective efficiency. The presence and structure of shared services and platforms provide strong support for the unit's scientific output. Additionally, the frequent organization of internal, local, and international meetings by unit members and the local community plays a crucial role in the training and development of master's and PhD students, as well as postdoctoral fellows.

RECOMMENDATIONS REGARDING THE EVALUATION AREA 2: THE UNIT'S SCIENTIFIC RESULTS, IMPACT AND ATTRACTIVENESS

To strengthen the team's critical mass and ensure its long-term sustainability, efforts should focus on recruiting additional Inserm permanent researchers (or CNRS through mobilities) and expanding the number of PhD students and postdoctoral fellows. This reinforcement will secure the continuity of expertise and foster a dynamic research environment. Particular attention should be given to consolidating mentorship and enhancing the visibility of early-career researchers, encouraging them to take leadership roles in project design and to achieve first-author publications. At the same time, it is essential to maintain a clear strategic focus, ensuring that the diversification of imaging modalities and biological models remains coherent and manageable within the team's core objectives.

RECOMMENDATIONS REGARDING EVALUATION AREA 3: INCLUSION OF RESEARCH ACTIVITIES IN SOCIETY

The Unit is encouraged to strengthen the strategic coordination and long-term structuring of its societal engagement activities. This includes developing a clearer governance framework to manage its expanding portfolio of industrial collaborations, start-up initiatives, and technology transfer actions, thereby securing the necessary administrative and managerial support to maintain both scientific productivity and innovation output. The unit should also establish a more systematic evaluation of the impact of its outreach and science communication activities, in order to optimize their effectiveness and better document their societal value. Furthermore, given the growing involvement of the unit in interdisciplinary, participatory, and European collaborative initiatives—illustrated notably by the SIGMA1 EUROPE COST Action, which enhances visibility and fosters dynamic networks at local, national, and international levels—continued institutional support will be essential to preserve momentum and capitalize on these opportunities. Strengthening internal coordination and ensuring adequate resources will help the unit sustain its positive trajectory and fully leverage its capacity to contribute to societal, economic, and biomedical innovation.

TEAM-BY-TEAM ANALYSIS

Team 1: Metabolic impacts and tauopathies
Name of the supervisor: Ms Nadine Mestre- Francés

THEMES OF THE TEAM

The team Metabolic impacts and tauopathies (Team 1) is focusing on how metabolic disturbances influence the development and progression of tauopathies, a category of neurodegenerative diseases characterized by the abnormal accumulation of tau protein in the brain. A key focus of the team is its 30-year breeding program for *Microcebus murinus* leveraging the species' long lifespan to conduct longitudinal studies on physiological aging and neuropathology. Other animal models (such as *Drosophila*, mouse and zebrafish) are also used to explore these mechanisms.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maitres de conférences et assimilés	4
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	5
Sous-total personnels permanents en activité	11
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels non permanents d'appui à la recherche	2
Post-doctorants	0
Doctorants	2
Sous-total personnels non permanents en activité	5
Total personnels	16

EVALUATION OF THE TEAM

Overall assessment of the team

The team made original contribution to the understanding of how metabolic changes influence neurodegeneration and has a very good to excellent track record of publication. Their work supports the development of novel interventions aimed at slowing or preventing disease progression using rational interdisciplinary approaches, combining molecular biology, genetics, and metabolic analysis. The team uses innovative preclinical models, including animal models such as *Microcebus murinus*, *Drosophila* (fruit fly) and mouse or zebrafish, to underlie the mechanisms of tauopathies and to identify potential metabolic biomarkers or therapeutic targets. The scientific objectives of the team are excellent, with significant potential for human and environmental health. However, the diversity in models and related projects might be hard to sustain in the future without the capacity to obtain other research grants. The team seems well-balanced between junior/senior researchers and receives significant technical support. It is led by a PI who gained local, national and international recognition throughout the years but will retire soon. Training through research is very good but can be improved regarding the number of researchers and the links with EPHE. The team faces substantial teaching duties for most members of the team including the team leader. To strengthen the main projects and to ensure their long-term sustainability, efforts should focus on recruiting additional permanent Inserm researchers and expanding the number of PhD students and postdoctoral fellows. Thus, the overall evaluation is **excellent**.

Context-related strengths and opportunities

This team specializes in studying brain aging and prion-type neurodegenerative diseases, such as Alzheimer's, using the lemur model. Their unique expertise lies in exploring metabolic mechanisms in tauopathies—a less-studied area compared to genetic or proteomic approaches. Their work integrates behavioral, imaging, and histological analyses, with publications in journals like *Brain Behavior*, *Scientific Reports*, and *Neurobiology of Aging*. The team has developed innovative pathological models using viral-based gene transfer, enabling early-stage disease induction and therapeutic testing. The team has fruitful internal collaborations with the other teams of the unit. Collaborations, especially with Team 3 on spinal cord injury, have led to successful strategies for mitigating cognitive and motor deficits. They have also established a valuable biological resource library, including a biobank of genomic DNA, plasma, and tissues, now accessible to the scientific community. The team also have several collaborations at the local, national and international levels and has built a very good international network.

The team uses diverse other animal models (*Drosophila*, zebrafish, mice, rats). Their research on REG-1alpha focuses on its role in Alzheimer's disease—specifically, its involvement in neurotoxic lesion development and its potential as a biomarker or therapeutic target. Key discoveries include REG-1alpha's role in neurogenesis, its interaction with Calpain-2 (depending on glycosylation), and its overexpression in early Alzheimer's stages, positioning it as a promising biomarker. These studies aim to uncover molecular mechanisms of neurodegeneration and advance diagnostic or therapeutic strategies for Alzheimer's and age-related diseases with publications in journals like *Cell Dev Biol*, *Neurobiol Aging* or *Brain Behav Immun*. It could be noted that the team is also part of biodemographic research, integrating demographic, biological, and social approaches to study aging and promote healthy longevity. Their work has advanced international databases, comparative centenarian studies, and health expectancy research, contributing significantly to aging studies and public health policies (Nat Comm, 2019; Nat Med, 2023; Eur J Public Health, 2024).

The team has been successful in obtaining a European grant with the ETAIN project (220 k€) which is a major European initiative to assess the impacts of electromagnetic fields on human and environmental health or a contract from industry (contract from Lab Biogen, 150 k€) as well as grants from EPHE. Regarding human resources, the team has recruited one EPHE engineer in 2023.

The team has an excellent implication in teaching activities with six researchers and 4 HDR, which should facilitate training through research.

Context-related weaknesses and risks

The team is highly specialized with a unique expertise and positioning, underpinned by a supportive research ecosystem driven by pressing clinical needs. Its key strengths include metabolic expertise, interdisciplinary collaboration, and a proven ability to translate basic research into clinical applications. However, the team's projects may face budgetary and resource constraints, potentially limiting the scale or pace of research, particularly for large-scale or longitudinal aging studies (e.g. those involving mouse lemurs). The funding of the team relies on two researchers including the team leader who will retire soon. There is only one international grant. Additionally, research using animal models—especially primates—is subject to stringent ethical and regulatory oversight. Shifts in regulations or public sentiment could further restrict the team's ability to conduct certain studies. Moreover, the team comprises only two HDR scientist among young tenured people. The team's visibility is rather modest and only attested by the participation of the leader and one member to international conferences' organization which reduce the chance to be able to attract excellent students. One PhD student will defend soon and one was recently hired. During the last term the team hosted no postdoctoral fellow.

It is important to mention that the team faces high teaching duties for all members, including the team leader. The team workforce also will also face two close retirements and has no full-time researcher. To ensure the successful execution of the many projects, to preserve the team's expertise, and expand its horizons with innovative approaches, a significant grouping of forces is essential. While the team's production is very good to excellent, there is room for improvements—both in volume and in the caliber of publications—by aiming for higher-impact journals, a goal well within reach given the significance and relevance of the team's research themes.

ANALYSIS OF THE TEAM'S TRAJECTORY

Most of the members of Team 1 after the retirement of the senior leaders will join the new DynaMo team while one member will join the PAON team. The trajectory of the team's members project in the new organization is coherent with their expertise's on Reg-1a in neurodegenerative disorders and environment on several pathologies. This change represents an opportunity to forge new strategic collaborations with high potential for societal impact.

Team 2: Cellular determinants of neuroprotection
Name of the supervisor: Mr Tangui Maurice

THEMES OF THE TEAM

The team Cellular determinants of neuroprotection is mostly focused on Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS) and Wolfram syndrome (WS), with the aim of developing disease-relevant preclinical models, identifying pathophysiological mechanisms in order to develop therapeutic targets and biomarkers. The team has a long-standing expertise on the Sigma-1 receptor and has uncovered some of its physiological roles and pathophysiological implications in AD and ALS, and more recently in WS.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maitres de conférences et assimilés	2
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	9
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels non permanents d'appui à la recherche	4
Post-doctorants	3
Doctorants	3
Sous-total personnels non permanents en activité	11
Total personnels	20

EVALUATION OF THE TEAM

Overall assessment of the team

The team is internationally recognized for its expertise on Sigma-1 receptor and neurodegenerative disorders. The capacity of the team to obtain funding for its project is commendable. The team has produced outstanding findings and was able to leverage its results from fundamental research through the development of a start-up and the filing of patents. The team has also been able to attract new members, including one researcher recruited at Inserm in 2024. The overall evaluation of the team is **outstanding**.

Context-related strengths and opportunities

Building on its previous work and expertise on the Sigma-1 receptor, the team has made major achievements by demonstrating the beneficial role of Sigma-1 receptor activation in preclinical models of WS and ALS/FTD models. These results were published in reference journals (Human Molecular Genetics 2020, Redox Biology 2022) and high-profile journals such as Science translational Medicine (2022) and Nature Communication (2020). These preclinical studies are integrated into a translational and economic valorization approach. Indeed, collaborations with medicinal chemistry groups allowed to identify new chemical entities and some lead compounds have been protected with patents granted. Economic valorization of this fundamental and preclinical research has also been achieved through the creation of a start-up. Building on finding published prior to this reference period (Science Signaling 2018), the team also identified NCS1 as an interactor of the

sigma-1 receptor and potential target for disease-modifying interventions (Science translational Medicine 2022, Molecular Therapy Methods & Clinical Development 2022), paving the way for an ongoing gene therapy preclinical project. The team has also identified pathophysiological mechanisms associated with some mutations identified in patients with WS, such as destabilization of mitochondria-associated endoplasmic reticulum membranes, impaired autophagy and mitophagy, as well as mechanisms responsible for the collapse of the endocytotic potential in WS. These findings were published in high profile journals (Cell Death & Disease 2023, Autophagy 2023). The team has been quite successful regarding research funding with a strong support (1M€) from the SATT AXLR for the creation of the start-up, 2 ANR/DFG grants (SIR-BUCHE-AS and SIRWOLFPHAGE as PI and in collaboration with Germany), 1 EU grant (Cost Action), several grants from foundations and associations (FRM, FRC, AFM, France Alzheimer, foundation pour l'audition), as well as several local grants (region Occitanie, EPHE, Univ Montpellier and CHU). Most of the grants have been obtained as PI. Regarding human resources, the team has recruited one Inserm researcher in 2024, one Inserm engineer (mobility from INM in 2020) and one EPHE engineer in 2023.

Context-related weaknesses and risks

Given the previous achievements of the team, its positioning and the successful valorization efforts, there is no major weakness or threat at the scientific level. The team has identified the risk associated with the fact that some members will retire during the next contract. The team is currently working on strategies, including European consortia to attract competitive candidates for Inserm positions, ATIP/Avenir or ERC starting grants.

ANALYSIS OF THE TEAM'S TRAJECTORY

The team's trajectory is coherently and strategically focused on key cellular mechanisms that operate in most neurodegenerative disorders such as endoplasmic reticulum stress, mitochondria associated and altered calcium homeostasis. These dysfunctional cellular processes will be investigated in a limited number of neurodegenerative models (AD, ALS, WS) and focusing on targets (Sigma-1 receptor, NSC1, Reg-1a) that are based on the team's expertise and previous works. The recent recruitment of an Inserm researcher in 2024 is an asset for the team and will contribute to the feasibility and success of the research program. There is a good balance between basic science and valorization opportunities. It will be crucial to thoughtfully organize the integration of Team 1 members to ensure their successful onboarding into this already successful team.

Team 3: Integrative biology of neuroregeneration
Name of the supervisor: Ms Florence Perrin

THEMES OF THE TEAM

The team Integrative biology of neuroregeneration (Team 3), arrived from INM in 2016, focuses on spinal cord injury (SCI) using a multidisciplinary and translational approach that combines behavioral studies, cell-specific transcriptomics, and advanced imaging (MRI, CARS, AFM, SHG). The team investigates the role of glial cells in limiting axonal regeneration and develops novel therapeutic strategies in mice and non-human primates. Their work centers on modulating the glial response, improving sensory-motor recovery assessments, and advancing bioimaging tools to evaluate regeneration and therapeutic outcomes.

CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

During the evaluation period, Team 3 took into account the recommendations of the previous report. In particular, the group strengthened the quality and visibility of its publications, with an increased number of first/last/corresponding-author articles in high-impact journals (Theranostics), reflecting an adapted publication strategy. The group continued to rely on validated experimental models while ensuring their cross-validation and translational relevance, supported by comparative and clinical approaches. Links with the University of Montpellier and the University Hospital were reinforced through embedded clinicians and active involvement in clinical research, notably on human spinal cord samples.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

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

EVALUATION OF THE TEAM

Overall assessment of the team

Team 3 presents a coherent, scientifically ambitious, and translationally relevant program. Its strengths lie in the integration of cellular, behavioral, and imaging approaches, its innovative view of glial biology, and its clinical perspective. Sustained institutional support and strategic reinforcement of human resources will be key to maintaining the team's upward trajectory and international competitiveness in the coming years. Thus, the overall evaluation is **very good to excellent**.

Context-related strengths and opportunities

The team benefits from recognized scientific leadership, notably through F. Perrin's appointment as Senior Member of the Institut Universitaire de France (2020–2025), and from strong institutional support that has fostered productive interdisciplinary collaborations with physicists, clinicians, and imaging specialists. Over the past five years, Team 3 has demonstrated clear and continuous scientific progression, successfully achieving all objectives set out in the previous contract. This resulted in 11 original research articles, including a publication in *Theranostics* (2021), 4 review articles, 3 clinical research papers, and 1 book chapter, reflecting both fundamental and translational expertise. In parallel, the team secured more than 400 k€ in competitive funding, including support from the IUF and the CHU Montpellier (COEN). The period was also marked by increasing scientific recognition, as illustrated by invitations to contribute editorials and the expansion of national and international collaborative networks. In addition, the team substantially strengthened its imaging and clinical research capacities by expanding advanced MRI and biophotonic approaches through close collaboration with physicists, and by developing a unique collection of human spinal cord samples, enabling the identification of age- and sex-dependent glial and myelin alterations. Finally, the development of new and innovative research axes, notably on sex dimorphism in spinal cord injury and supraspinal consequences of injury, together with original concepts such as Fgfr4-mediated modulation of astrocyte plasticity and sex-dependent glial mechanisms, highlights the team's strong capacity for innovation and positions it for enhanced scientific impact and international visibility.

Context-related weaknesses and risks

Despite its scientific quality and translational potential, the team faces several structural limitations. The absence of an Inserm researcher and a very small number of PhD students (only one currently) pose a risk for sustainability and renewal of human resources. While scientific production is fair (11 recent publications, including high-impact works, 4 review articles, 3 clinical research articles and 1 book chapter), the limited number of first-author papers from young researchers indicates a possible imbalance in mentoring or workload distribution.

The high technical and methodological diversity of the program—spanning rodent, primate, and human models—may also stretch resources and increase dependency on external collaborations. Finally, the ambitious translational objectives may be challenging to sustain without additional permanent staff or technical support dedicated to imaging and bioinformatics.

ANALYSIS OF THE TEAM'S TRAJECTORY

The trajectory indicates a maturing, high-potential team with a strong translational vision. The gradual integration of clinical imaging and cross-species comparative studies further reinforces its position as a bridge between basic neuroscience and clinical neurology. The team should strengthen its human resources by recruiting a permanent researcher (e.g. Inserm) and increasing the number of PhD students, in order to secure sustainability, improve mentoring, and rebalance scientific contributions from early-career researchers. Given the breadth and technical complexity of the research program, clearer prioritization of research axes and the allocation of dedicated technical support, particularly in imaging and bioinformatics, are strongly recommended to ensure feasibility and autonomy. Finally, Group 3 faces a significant challenge regarding its integration within the future organizational structure of the Unit. Indeed, the positioning of the team within the new organizational structure must be clarified, in order to reinforce scientific coherence, enhance synergies of the new groups, and secure visibility and impact.

Team 4: Environmental impact in Alzheimer's disease
 Name of the supervisors: Ms Catherine Desrumaux and Mr Laurent Givalois

THEMES OF THE TEAM

The team Environmental impact in Alzheimer's disease (Team 4) of the MMDN is studying the environmental impact of Alzheimer's disease. The team is focusing on characterizing the impact of oxidative stress and carbonyl stress (COS), two types of stress linked to exposure to reactive compounds found in fried foods, cigarette smoke, and exhaust fumes. To do this, *in vivo* and *in vitro* models are used to assess the role of COS in the etiology of the disease. The team also tests innovative preventive and therapeutic strategies.

TEAM WORKFORCE: IN PHYSICAL PEOPLE AS OF 31/12/2024

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

EVALUATION OF THE TEAM

Overall assessment of the team

Team 4, quite small presents a scientifically ambitious and relevant program investigating how environmental factors shape the pathophysiology of Alzheimer's disease through *in vivo* and *in vitro* approaches, and develops innovative therapeutic strategies to counter their effects. This coherent and multidisciplinary program is scientifically robust, though its limited personnel constrain its ambitions; reinforcing the team would support its objectives and strengthen its international visibility. The study of combined environmental exposures and their impact on neurodegeneration is an expanding field. By focusing on mechanistic insights within this emerging domain, the team has a genuine opportunity to strengthen its positioning and contribute significantly to advances in understanding and mitigating neurodegenerative processes. Thus, the overall evaluation is **very good to excellent**.

Context-related strengths and opportunities

Team 4 has structured its research around four major objectives. The first one concerns Glucocorticoids and Alzheimer's disease (AD). The team investigated the involvement of the stress axis, particularly the hypothalamic-pituitary-adrenal axis, by analysing glucocorticoid receptors (GRs) and their contribution to disease mechanisms. Their work also explored therapeutic approaches based on selective GR modulators, with the aim of limiting or delaying AD progression. The second one deals with oxidative stress, neuroinflammation, and lipophenols. In particular, team members examine the neuroprotective effects of omega-3 polyunsaturated

fatty acids, especially DHA, which is essential for brain development and cognitive function. Their studies demonstrated that intranasal DHA administration reduces oxidative stress and neuroinflammation in AD models. In parallel, hybrid molecules such as lipophenols showed promising neuroprotective properties, improving cognitive performance in vitro and offering new pharmacological perspectives. The third address the links between epilepsy and neurodegeneration. Depending on the age at onset, epileptic episodes may increase the risk of developing AD. Using mouse models, the researchers identified biomarkers associated with AD and assessed their therapeutic and modulatory potential. Their work revealed pathways through which controlling neuroinflammation related to epilepsy could help mitigate long-term neurodegenerative processes. Finally, the team explores oscillatory neuronal activity and cognitive impairment. By using photopharmacological tools to modulate glutamatergic neuron activity in the hippocampus, Team 4 aims to restore functional oscillations and alleviate AD-related cognitive deficits. Despite its limited size, Team 4 has successfully advanced knowledge on how environmental factors, such as pesticide exposure and chronic stress, affect lipid metabolism and contribute to AD onset. Through sophisticated behavioral models and detailed molecular and histological analyses, the team identified multiple alterations, including disruption of oxidative balance, carbonyl stress leading to neuroinflammation (notably GFAP, IL-10, and GC modifications), amyloid aggregation associated with HPA axis dysfunction, and ultimately neuronal death. These findings collectively strengthen the evidence that environmental exposures significantly increase vulnerability to Alzheimer's disease and highlight the relevance of the team's mechanistic and therapeutic investigations. Team 4 demonstrates a good level of productivity, particularly considering its limited size. The team has produced 16 original research articles in high visibility journals (Neuroendocrinology, FASEB, Antioxidants). The production activity relies on an excellent fundraising skills at the national level (2 ANR, Fondation pour la Recherche Médicale, France Alzheimer,...). In addition, it has contributed 5 review articles (ADRs), and has filed 1 patent, further highlighting its capacity for innovation. The team has also maintained an active presence in the scientific community through 11 conference communications, supporting both visibility and knowledge dissemination. The group's ability to recruit two PhD students and one postdoctoral researcher demonstrates its attractiveness over the period in question.

Context-related weaknesses and risks

Although the team's scientific expertise is clearly supported by the quality of its publications, several weaknesses limit the full impact of its research. First, collaboration with clinical researchers and epidemiologists remains insufficient. Such partnerships would be essential to evaluate the translational potential of the team's findings, particularly regarding the real-world health risks associated with the environmental exposures studied. Strengthening these connections would help bridge the gap between experimental results and their applicability to human populations.

The team also faces a shortage of doctoral candidates and lacks stable technical and scientific support. Much of the assistance currently relies on temporary contracts, which affects the continuity and long-term sustainability of the human resources needed to carry out ambitious research programs. This fragility in staffing reduces the team's capacity to maintain momentum and fully exploit its methodological expertise.

From a structural standpoint, Team 4 has undertaken relevant but somewhat dispersed research themes. With a small group of investigators, pursuing such a wide range of topics dilutes efforts and hinders the consistent achievement of all objectives. A more focused strategy—centering on specific cellular and molecular mechanisms within a narrower thematic field—could have strengthened coherence, improved productivity, and increased overall impact.

Moreover, the team's interest in natural compounds as therapeutic or preventive approaches raises methodological concerns. While promising, these strategies require rigorous toxicological evaluations before any pharmacological or translational development. The absence of preliminary toxicology studies limits the potential for these compounds to progress toward applications in human health and reduces the credibility of their therapeutic promise.

In summary, despite its strong scientific foundation and innovative approaches, the team would benefit from increased clinical and epidemiological integration, more stable human resources, a clearer thematic focus, and strengthened methodological frameworks for the development of natural compounds.

ANALYSIS OF THE TEAM'S TRAJECTORY

Team 4 has positioned itself on a highly promising research axis by elucidating the reciprocal interactions between brain dysfunction, internal physiological processes, and external environmental exposures. The team's numerous discoveries in these areas, published in high-quality journals, attest to its scientific vitality and its capacity to advance innovative concepts in neurodegeneration. Its national and international partnerships, as well as the support it has secured, have significantly enhanced its visibility and impact within the scientific community. The development of original therapeutic strategies, ranging from gene-based approaches to the exploration of new natural or hybrid biomolecules, further reinforces the team's appeal for industrial partners.

These activities create promising pathways for technology transfer, offering potential for added value and concrete applications derived from the scientific results obtained.

Overall, the strategic orientation toward translational and industrial applications strengthens its standing and underscore the relevance of its research program that will be integrated into the new DYNAMO team for the next contract. This change represents an opportunity to forge new strategic collaborations with high potential for societal impact.

CONDUCT OF THE INTERVIEWS

DATE

Beginning: 05 November 2025 at 09:00

Ending: 05 November 2025 at 16:30

Interview conducted: on-site or remotely

PROGRAMME OF THE INTERVIEWS

8:30-8:45 Huis Clos du comité en présence de CS Hcéres
Salle A36.01

8:45-9:00 Présentation du processus d'évaluation par le conseiller Hcéres et du comité d'experts
• Salle A36.01

9:00-11:55 Présentation de l'Unité et de ses thématiques de recherche (réunions publiques)
Salle A36.01

09:00-9:40 : Présentation de l'unité avec les principales réalisations et le projet/la trajectoire par le directeur de l'Unité MMDN, le Dr **T. Maurice** (20 min de présentation + 20 min de discussion)

9:40-10:05 : Présentation de la thématique « Metabolic impacts and tauopathies » par **N. Mestres-Francès** (15 min de présentation + 10 min de discussion)

10:05-10:20 *Pause*

10:20-10:45 : Présentation de la thématique « Integrative biology of neuroregeneration » par **F. Perrin** (15 min de présentation + 10 min de discussion)

10:45-11:10 : Présentation de la thématique « Environmental impact in Alzheimer's disease » par **C. Desrumaux et L. Givalois** (15 min de présentation + 10 min de discussion)

11:10-11:35 : Présentation de la thématique « Cellular determinants of neuroprotection » par **T. Maurice** (15 min de présentation + 10 min de discussion)

11:35-11:55 : **Présentation de la trajectoire par le porteur de projet (B. Delprat)** (10 min de présentation + 10 min de discussion)

11:55-12:20 *Visite des plateformes avec le personnel*

12:20-13:30 *Pause déjeuner (Salle Verdier, bâtiment 24)*

13:30-14:30 Discussions à huis clos avec les différentes catégories de personnels
• Salle des Actes, bâtiment 7

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 chef d'équipe)

15:00-15:15 **Réunions à huis-clos du jury pour préparer les échanges/questions avec DU et tutelles**
o Salle des Actes, bâtiment 7

15:15-15:45 Discussion avec le DU
• Salle des Actes, bâtiment 7

15:45-16:00 *Pause*

16:00-16:30 Discussion avec les représentants des organismes de gestion/tutelles
• Salle des Actes, bâtiment 7

16:30-17:00 **Réunion privée du comité de visite en vue de la préparation du rapport (huis-clos)**
• Salle des Actes, bâtiment 7

17:00 *Fin de la visite*

GENERAL OBSERVATIONS OF THE SUPERVISORS



UNIVERSITÉ DE
MONTPELLIER

MONTPELLIER
Le 25 février 2026

Monsieur Arnaud TOURIN
Directeur du Département d'évaluation de la recherche
HCERES
19 rue Poissonnière I 75002 PARIS

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OBJET : Rapport d'évaluation - DER-PUR270025826 - MMDN - Mécanismes Moléculaires dans les Démences Neurodégénératives

Monsieur le Directeur,

Je tiens à remercier le comité de visite HCERES pour la qualité de son rapport d'évaluation concernant l'unité de recherche MMDN - Mécanismes Moléculaires dans les Démences Neurodégénératives - dirigée par Monsieur Tanguy MAURICE.

Le directeur de l'unité, l'EPHE et moi-même avons pris connaissance des recommandations formulées par le comité de visite.

Vous trouverez ci-après les observations de portée générale du directeur de l'unité et de l'EPHE.

Nous vous prions d'agréer, Monsieur le Directeur, nos salutations distinguées.

La Vice-Présidente chargée de la recherche

Agnès MIGNOT

Unité de recherche UMR_S1198
Mixte avec l'Université de Montpellier et l'EPHE
*Mécanismes moléculaires dans les démences
neurodégénératives*
Tangui MAURICE, directeur



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Ref: DER-PUR270025826- MMDN - Mécanismes Moléculaires dans les Démences
Neurodégénératives

Dear Experts of the HCERES committee,

We thank you for the thorough and expert analysis you conducted on the scientific activity of the MMDN laboratory.

We were surprised that the high level of international exchanges and welcoming of visiting scientists (including co-directed PhD theses with Cuba, Georgia and Germany) was not appreciated as we expected. We benefited from 8 PHC Campus France, 2 DAAD and BayFrance and 1 Adelante2 exchange programs during the period and, more recently, from short-term scientific missions funded by the Cost Action. A rapid check in our production list showed that 18 of the 123 original articles of our list are directly resulting from research stays of foreign researchers in the lab. These visits had already a significant impact on our production and this trend will be strengthening in the coming years.

Beside this only remark, we appreciated the accuracy of your analyses and the thoughtfulness of your recommendations, which we will do everything to implement during the next term of office.

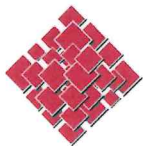
On behalf of all MMDN personnels,

Tangui Maurice



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Paris, le 16 février 2026

Réf. : MH / JB / RB / 2026 - 013

Objet : demande de retour des observations des tutelles sur le rapport d'évaluation - DER-PUR270025826 - MMDN - Mécanismes Moléculaires dans les Démences Neurodégénératives

L'EPHE remercie le comité de visite du HCERES pour le rapport sur cette unité et n'a pas de remarque particulière à formuler.

Michel HOCHMANN
Président de l'École Pratique des Hautes Études

Evaluation of universities and schools
Evaluation of research units
Evaluation of the academic formations
Evaluation of the national research organisms
Evaluation and International accreditation



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