MMDN - Mécanismes moléculaires dans les démences neurodégénératives

Rapport Hcéres

agence d'évaluation de la recherche
et de l'enseignement supérieur

Department for the evaluation of research units

AERES report on unit:

Molecular Mechanisms in Neurodegenerative Diseases

MMDN

Under the supervision of the following institutions and research bodies:

Nouvelle Université de Montpellier

École Pratique des Hautes Études - EPHE

Institut National de la Santé Et de la Recherche Médicale - INSERM

January 2014

agence d'évaluation de la recherche
et de l'enseignement supérieur

Department for the evaluation of research units

On behalf of AERES, pursuant to the Decree of 3 november 2006[1]*,*

- Mr. Didier HOUSSIN, president
- Mr. Pierre GLAUDES, head of the evaluation of research units department

On behalf of the expert committee,

- Mr Jean Christophe CASSEL, chair of the committee

[1] The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n ° 2006-1334 of 3 November 2006, as amended).

Evaluation report

This report is the result of the evaluation by the experts committee,the composition of which is specified below.

The assessment contained herein are the expression of independent and collegial deliberation of the committee.

Unit name:	Molecular Mechanisms in Neurodegenerative Diseases
Unit acronym:	MMDN
Label requested:	INSERM
Present no.:	UMR_S 710
Name of Director (2013-2014):	Mr Jean-Michel VERDIER
Name of Project Leader (2015-2019):	Mr Jean-Michel VERDIER

Expert committee members

Chair: Mr Jean Christophe CASSEL, Université de Strasbourg

Experts:

Mr Bernard FAUCONNEAU, Pôle Biologie Santé, Poitiers

Mr Damien GALANAUD (representative of CSS INSERM)

Mr Peter HEUTINK, German Center for Neurodegenerative diseases, Tübingen, Germany

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Mr Jérôme TROUSLARD (representative of CNU)

Scientific delegate representing the AERES:

Mr Yves TROTTER

Representatives of the unit's supervising institutions and bodies:

Mr Hubert BOST, École Pratique des Hautes Études

Mr Michel DESARMENIEN (representative of Doctorale School ED n° 168 from Université Montpellier 2)

Mr Bernard GODELLE, Université Montpellier 2 – Sciences et Techniques

Ms Hélène GROS-DAGNAC (representative of ITA from CSS8 of INSERM)

Mr Philip HUYSE (representative of Doctorale School ED n° 472 from EPHE)

Ms Marie-Josèphe LEROY-ZAMIA, Chargée de Mission, Département de l'Évaluation et du Suivi des Programmes

1 • Introduction

History and geographical location of the unit

The MMDN laboratory has been created *ex nihilo* in January 2005 as a research unit jointly supported by INSERM (Institut National de la Santé et de la Recherche Médicale), UM2 (Université Montpellier 2) and EPHE (École Pratique des Hautes Études). It is located on the campus of the Université Montpellier 2 and belongs to the Department of Health & Biology (head: Mr Jean-Michel VERDIER), which includes 11 laboratories or institutes.

At its foundation in 2005, the MMDN laboratory was evaluated by the Scientific Commission CSS7 of INSERM (Technologies pour la Santé, Thérapeutiques, Biotechnologies, now CSS8). At this time, the MMDN included 4 permanent staff under the supervision of Mr Jean-Michel VERDIER. In July 2005, a new team joined the laboratory, headed by Mr Tangui MAURICE. Eighteen new members have joined either team over the following 6 years. In January 2011, it was decided to initiate a third team co-headed by Ms Véronique PERRIER, previously in team 1, and Ms Mireille ROSSEL, who joined the lab project at that time. In January 2012, a new team (team 4) headed by Mr Jean-Marie ROBINE, and dedicated to public health in the field of ageing, joined the project. Finally, a team headed by Ms Florence MASCHAT joined the project most recently.

At the onset, the primary focus of the laboratory was to develop biotechnological, diagnostic and/or therapeutic approaches dedicated to the study of neurodegenerative disorders (Alzheimer, Parkinson, Prion diseases), hence the name of the laboratory. This scope has progressively broadened to include the study of ageing *per se*. In this context, the arrival of team 4 has been appropriate and sound, all the more because it carried the most welcome opportunity to combine public health and life sciences, to achieve interdisciplinarity, and to provide access to human cohorts. In parallel the range of experimental models (Alzheimer's, prion and Parkinson's disease) has also expanded and now includes a large panel of animal models (mutant and wild-type zebrafish, transgenic and wild type rodents, lemurian primate) as well as cellular models. The fifth team having joined the project brought in expertise on relevant models of Huntington's disease.

Today, MMDN is an interdisciplinary lab dedicated to research on the biology of ageing and of neurodegenerative diseases, from cells to humans. One major strength of this lab is to bring together researchers working on human ageing, Alzheimer's disease (AD), Parkinson's disease (PD), prion, and Huntington's (in the next 5-year plan) diseases, as well as on protein folding, a process of utmost importance in all these neurodegenerative disorders.

Because particular emphasis is being placed on developing cross-disciplinary approaches, MMDN lab is primarily affiliated to CSS8 of INSERM « Technologies pour la santé, Thérapeutiques, Biotechnologies », and secondarily to CSS6 « Neurosciences, Cognition, Santé Mentale », which is perfectly sound, not only in a historical dimension, but also for the future.

Management team

Director: Mr Jean-Michel VERDIER

Team 1: Ms Nadine MESTRE-FRANCES and Mr Jean-Michel VERDIER

Team 2: Mr Tangui MAURICE

Team 3: Ms Véronique PERRIER and Ms Mireille ROSSEL

Team 4: Mr Jean-Marie ROBINE

Team 5: Ms Florence MASCHAT

AERES nomenclature

Main field: SVE1 Biology, health.

Main sub-field: SVE1_LS5 Neurobiology.

Secondary sub-fields: 1. SVE1_LS2 Genetics, Genomics, Bioinformatics;

2. SVE1_LS7 Epidemiology, Public health, Clinical research, Biomedical technologies.

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	10	10
N2: Permanent researchers from Institutions and similar positions	6	7
N3: Other permanent staff (without research duties)	7	8
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	1 (DREM) + 6 (Post-docs) + 1 (visitor)	1 (DREM) + 1 (Post-doc)
N6: Other contractual staff (without research duties)	5	3
TOTAL N1 to N6	**36**	**30**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	5	
Theses defended	14	
Postdoctoral students having spent at least 12 months in the unit*	10	
Number of Research Supervisor Qualifications (HDR) taken	4	
Qualified research supervisors (with an HDR) or similar positions	12	14

2 • Assessment of the unit

Strengths and opportunities related to the context

First, the lab is now well known for its unique primate model and for its investigations of discoveries on Sigma proteins.

Second, regarding the work on neurodegenerative diseases and protein folding/misfolding, the multiplicity of animal models enabling investigations at different levels of analysis is a real strength, at least as long as the risk of scientific dispersion is contained (the risk exists). The lab does a real work in order not only to further develop these models (e.g., drosophila, zebra fish) but also to optimize approaches according to the complementarity of the models.

Third, the fact that the work carried out by this laboratory reaches national and international competitiveness is not only attested by a very good amount of publications in international journals, but also by the latter's quality (slightly less than 1 out of 5 has been published in a journal having an IF > 6). This competitiveness is also supported by the impressive amount of external funds raised during the past contract (only about 18 % of the aggregated budget corresponds to recurrent funding).

Fourth, the past contract indicates a very good attractiveness for doctoral students and post-docs, although the current statistics are pointing to a possible decrease to which attention should be paid (it is to be noticed that the number of doctoral fellowships is relatively low, one of the reasons being that the Région Languedoc-Roussillon has not provided any such identified doctoral fellowships for several years).

Last but not least, several researchers of the laboratory have excellent and efficient collaboration networks with the industry, which, given the research topics developed, is all but a surprise. Some of these researchers have even created their own startup with a significant number of employees. This supports an engagement of lab members in the economical development of the local territory. The overall research topic of the laboratory, which could be summarized as "neurodegeneration and aging", is a very competitive one at both national and international levels, with a potential for very high societal impacts of research and genuine technological development with significant relations with public health issues. Fundings raised over the past demonstrate that the MMDN is on the side of the winners despite the burden of this competitiveness. It is also to note that the Université Montpellier 2 and the École Pratique des Hautes Études provide an unreserved support to the laboratory, especially in terms of human resources, but not only.

Weaknesses and threats related to the context

First, given its past and currently running recognition by INSERM, which is the national research institute dealing specifically with medical issues, it is surprising that interactions with the hospital and clinical worlds, especially in the fields of neurology, have been so limited thus far (is it a problem of environment or a political option? Probably a bit of both).

Second, although the quality of publications is very good, there seems to be some room for increasing the number in high impact factor journals. However, while this is often considered a quest for a holy grail in many places, it is not an absolute redemption criterion for scientific quality.

Third, if the will of the lab head, together with that of his lab members, is to continue efforts towards further expansion of the laboratory and its staff, then it seems that a limited capacity for animal accommodation in the Université Montpellier 2 might become a disabling factor.

Fourth, if one considers the number of qualified research supervisors (HDR; currently 12), the number of ongoing PhDs may seem quite low (currently 4, as indicated in the report, and 6 during the visit).

Fifth, as it is presented in the project, there is a potential for relatively strong interactions between some teams. However, and even if one considers that team 4 joined the lab only a couple of years ago (2012) and that team 5 has integrated the project most recently, past activity of the laboratory only led to 9 inter-team publications out of 127 peer-reviewed publications. This is less than 10 %, which is probably to be regarded as much too few given that the overall strength of a research unit should be more than the strict summation of its individual elements/potentials.

Sixth, the rationale for the presence of team 4 did not appear as naturally sound in terms of overall scientific strategy of the unit. But the experts committee has recognized that it brings an added value in terms of international

fame. Furthermore, the objective to apply exploration methods and statistical approaches/computations specific to aged human, or simply human cohorts in general, to colonies of ageing animals of different species (microcebus, mouse, zebra fish, and fly) is a real challenge that could lead to extremely original approaches.

Finally, the ratio between permanent technical staff and permanent researchers is very uneven from one team to another (e.g., close to 1 in team 1 and to 0,1 in team 2). This imbalance should require all attention by the unit head. Still in relation with this issue, a need for two additional positions (one for animal care and one for more general technical work) has been clearly identified, a point which has been largely echoed during the discussion with the technicians and engineers of the unit. Finally, teams 4 and 5 are headed by PIs who are going slowly towards their retirement time. Whether these teams are to be maintained afterwards and who might then take over should become a real concern as this question requires a preparation to be started from now on.

Recommendations:

- keep focused;

- do whatever is possible to establish and then strengthen relationships with medical teams in Montpellier (or from other cities within the région);

- if possible, try to increase the number of PhD students to at least half as much as the number of qualified supervisors;

- initiate significant efforts towards a better inter-team balance in terms of technical support;

- increase inter-team interactions, perhaps by allocating dedicated financial support, especially where different models can be used complementarily to generate original knowledge or/and test potential treatments. Try to use the inter-team interaction opportunities to achieve publications in journals with high impact factor;

- should teams 4 and 5, or their expertise, be essential to the unit's scientific strategy, all possible efforts should be made in order to ensure the continued existence of the specificity of their respective approaches as well as of the related expertise. This seems to be requiring well-thought recruitments;

- increase animal accommodation facilities to a level compatible with the scientific ambitions of the research unit.

3 • Detailed assessments

Assessment of scientific quality and outputs

Most activity of the laboratory concerns academic research (about 75 %), as indicated in the activity profile of the research unit, and focuses, by a way or another, on problems related to ageing (thereby agreeing with WHO (World Health Organization), EEC and national concerns). Over the past 5 years, the laboratory has had an output which, regarding publications, is very good, both in terms of quantity and quality, especially if one considers that many efforts have been accumulated to expand research forces. Indeed, 127 articles have been published in international peer-reviewed journals, with impact factors ranging from less than 3 to up to 38,3, the average being of about 5; about 1 out of 5 publications has been published in a journal with an IF > 6. This is an appreciable productivity with regard to the number of researchers having teaching duties (n = 10). While the production of teams 1 and 2 can be easily tracked, and this is also the case for the newly arrived team 4, it is more difficult to have a clear read out for teams 3 and 5. The past production of people in these teams is very good, but the impact of past co-authors of the team leaders who have left (retirement) or who did not join the unit project cannot be appreciated in all dimensions. The overall very good output in terms of publications is well paralleled by an important number of oral communications on invitation in either national or international congresses (n = 77). The unit has a leading position on several topics or knowing how, including the development of a new pathologic prion test (which has been validated in humans with Creutzfeldt-Jakob disease), the development of a primate model for aging (with about 300 non-human primates available currently), the use of a novel neurotrophic factor (Reg1α) as a biomarker for neurodegenerative diseases like Alzheimer's disease, and the validation of neuroprotective effects of mixed cholinergic/sigma-1 drugs in murine models of Alzheimer's disease. Research activity in one or the other of these domains has led to 3 patents and 1 proprietary know-how license. Although the link to the heart of the unit project is less obvious than the just mentioned elements, the knowing-how, expertise and worldwide scientific network of the head of team 4 might be considered a genuine added value with high-level challenging possibilities (but is there a real will to develop this option ?), especially if the project on longevity in animal models (zebrafish and mice being the less unrealistic ones) reveals feasible.

Assessment of the unit's academic reputation and appeal

The unit's academic reputation and appeal are supported by several indicators:

- first, over the past contract, 14 PhDs have been defended and 6 are going on. Regarding the strong competition for fellowships in Montpellier (and the lack of regional support in this regard), this is an acceptable achievement. The unit has also attracted a significant number of post-doctoral fellows;

- second, during the same time, there have been 30 visiting professors, for periods of from a few days to several months, which is an excellent achievement;

- third, several "senior" researchers are involved in international exchange programs and have been invited for conferences in european and other universities;

- fourth, there are a significant number of participations by qualified supervisors (HDR) to jurys of HDR, of PhD defenses or of thesis committees;

- fifth, the local reputation of the unit is nourished by contributions of its members to teaching programs and vulgarization events;

- sixth, the unit has received financial support from several "academic" funding bodies (e.g., CNRS, Université de Montpellier, ANR, etc in France, NIH and european contracts abroad) and has a solid national and international collaboration network;

- seventh, the unit is involved in 2 Labex (Lipstick and Numev);

- eighth, via team 4, the unit is involved in the coordination of two international networks (REVES & EHLEIS);

- finally, most "senior" team members are reviewers for national or international grant applications or/and for scientific journals.

Assessment of the unit's interaction with the social, economic and cultural environment

Concerning the economical environment, and although this first remark does not evenly apply to all teams, it must be emphasized that the unit has gathered several industrial contracts (total amount about 500 k€), is implicated in consultancies and advisory boards, has been the "support-cradle" of a start-up creation (Amylgen) as well as of the ex nihilo building of an institute devoted to the study of ageing (ITEV), and it has obtained several patents (INSERM).

Concerning the social and cultural environment, the following realizations can be brought to the credit of the unit: a regular collaboration with the media (french TV or EEC shooting videoclip), a large number of public lecture participations or participations to debate-conferences, a significant implication in the organization of and participation in the "Semaine du Cerveau", a participation in prospective studies on aging for the account of local authorities, the animation of the CompAn behavioral phenotyping platform.

Assessment of the unit's organisation and life

The unit is well organized and its life appears to be respecting a series of well defined rules. From a financial point of view, 20 % from all contracts are, when possible, withdrawn by the head of the lab and used for the overall functioning of the lab (e.g., rental, subscriptions, photocopier, common equipment, consumables, etc). In terms of everyday life, the laboratory will be organized in 5 teams with well-defined research topics in each, and several inter-team interaction opportunities that should lead to publications regrouping authors from more than only one team. All teams have subscribed to an organization chart that is joined to the application document in its annexes. There are regular meetings of the laboratory council, in which all categories of personnels are represented, including PhDs. This council discussed the strategic priorities of the unit's research plan, as well as recruitments and investments. All team leaders are informed about these meetings and their content, and of the resulting decisions. In addition to these meetings, there are meetings organized within each team as frequently as decided therein, as well as regular lab meetings, which take place twice a month. Finally, each month, there is a scientific meeting to which external scientists are invited in order to present their work. Once a year, there is a 1-day meeting where all researchers present their work to the whole laboratory, including secretaries, technicians and students. Researchers having no grants are supported during their "more difficult" times. This policy appears extremely appropriate and should be favorable to scientifically-constructive interactions, at least significantly more than over the past. At a scientific point of view, and in terms of interactions, the major difficulties might come from team 4 given the peculiarity of its research topic and expertise with respect to that of the other teams. Indeed, so far this topic has only concerned human population ageing and demographic aspects related to longevity (but see remarks above concerning the challenging dimension of this situation).

Assessment of the unit's involvement in training through research

The unit's involvement in training through research is evident at several levels:

- first, EPHE researchers with teaching duties are in priority involved in teaching at the level of Master's degree;

- second, 16 PhD theses have been defended over the last contract, which, given environmental factors and political options (see above), is reasonable. To this respect, both Doctoral Schools (EPHE and Université de Montpellier) have expressed strong support to this unit and their will to go on with that. The unit has also welcome several post-doctoral fellows;

- third, the unit is at the origin of several teaching modules for master students, dealing with cellular and molecular biology or/and ageing and senescence. Of particular merit is the implication of researchers having no teaching duties (INSERM or CNRS) in lectures and practical training at both Licence and Master levels; this is not an automatic implication in many research units over the French landscape.

Assessment of the strategy and the five-year plan

The laboratory has constructed over the past years on biotechnological, diagnostic and therapeutic approaches in relation with neurodegenerative diseases/disorders (mainly prion-related, Alzheimer's and Parkinson's diseases). This construction has been fruitful at various levels (novel diagnostic tool for pathological prions or Alzheimer's disease, full maturation of a primate model to investigate ageing, novel therapeutic potential for Alzheimer's disease, several patents, etc without forgetting a very good level of publications). These realizations are in good line with the

overall evaluation that had been made by the AERES experts committee in 2010 (mark was A for all teams and for the research unit). Over this period, the laboratory has been very attractive, as accounted for by its growth. This growth logically led to a reorganization of the research forces in 3 teams (the essential change being a strategic scission of team 1 into teams 1 and 3 of the new project) that were joined by two other teams identified as 4 and 5 in the new project. The former contract primarily affiliated the research unit to CSS8 (Technologies pour la Santé, thérapeutiques, biotechnologies) of INSERM, which was clearly sound, and to CSS6 (Neurosciences, cognition, santé mentale), which is sound as well, and perhaps even a bit more now if one considers in detail the content of the next 5-year project. However, the new project still constructs on biotechnologies and therapeutic options for neurodegenerative diseases, at least in the teams with a strong biological concern and an excellent expertise in biological approaches on physiopathological models. Several strong points can be derived from the project:

1) the microcebus model is now fully developed and should generate a large series of strong results in the future. In addition, team 1 has acquired leadership as regards the characterization of this model, at different organizational and functional levels, including cognition. The project of team 1 is well structured, both in terms of scientific priorities and supporting research forces, to achieve this horizon and to articulate some of its approaches to expertise present in other teams;

2) now, the process of aging and its normal and pathological correlates can be questioned at different levels of analysis with models going from the cellular to the sociological and demographic levels, with intermediate steps where drosophila, zebrafish, various tg mice and non-human primate models are well positioned in a phylogenetical continuity; well used, this can become a long and powerful wave on which the unit could be surfing with much success;

3) teams 1, 2 and 3 have a very good interaction potential, which could be easily extended to team 5, and these interactions could lead to a fruitful combinatory of the advantages of each model;

4) given the support of both EPHE and Université Montpellier 2, the expertise now present in the laboratory, the complementarity of models and approaches used, the laboratory should keep and perhaps even further increase both its attractivity and international recognition, which, with the exception of team 4, seems to have remained underneath its real potential so far;

5) given the content of the project of the unit for the 2015-2019 period, the high visibility of the unit for pharmaceutical companies and the already existing network, which is impressive, especially in team 2, should remain a genuine strength. Finally, all members of the experts committee have considered that, beyond the worldwide fame of team 4 and its very high level of some publications, the rationale of its integration in the unit project should be made more clear than has been in the written documents as well as during the on-site evaluation.

4 • Team-by-team analysis

Team 1: Cerebral Ageing & Neurodegenerative Diseases

Name of team leader: Ms Nadine MESTRE-FRANCES and Mr Jean-Michel VERDIER

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	6	5
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)	4	4
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1 (DREM) + 2 (Post-docs)	1 (DREM)
N6: Other contractual staff (without research duties)	2	
TOTAL N1 to N6	**16**	**11**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	7	6

• Detailed assessments

Assessment of scientific quality and outputs

This team has an international recognition for its skill on non-human primate (NHP) models by using *Microcebus murinus* (MIM). During the last 5-year period, this team developed an AD-like line in MIM, which represents an indisputable originality in AD (Alzheimer disease) models.

The members studied the transcriptomic profile of healthy old animals and AD-like animals and demonstrated clearly two distinct processes.

Moreover, they developed an Aß derivative vaccine ($K6A\beta_{1-30}$) for immunization in old primates, with high tolerance and interesting results on both cognitive performance and Aß burden.

This team acquired an important know-how on gene expression technics and establishment of a sustainable colony of MIM. They extended MIM utilization by developing 2 other relevant models: PD by gene transfer in the brain and a model of prion disease, with a possibility of oral contamination, which is especially adapted to study bovine spongiform encephalopathy

During the last 5-year period, this work has led to 31 papers with a mean impact factor of 4.8 (and an increased number of articles with an IF>6), 30 oral communications and 35 posters in national or international congresses, 7 conferences on invitation from abroad. Some papers were published in journals with high impact factors such as: 2 PNAS (9,7), J. Neurosci (7.2), Neurobiol. Aging (6.2).

It represents a good output for the team, which made a very significant contribution to the development of animal models of neurodegenerative diseases.

Altogether, this represents a pretty good production, taking into account the fact that the team's members spent significant effort to the development of animal models of neurodegenerative diseases.

Assessment of the unit's academic reputation and appeal

Team 1 obtained 4 international and 3 national grants since 2008. Among them, there are two European grants and a contract with NIH. This aspect must be emphasized because it is very rare for a French team to get NIH support. Most of the members are reviewers for scientific journals and national or international grants. Furthermore, the team welcomes each year foreign scientists from China, Europe or USA. It has mentored 6 PhD and 22 masters students.

These results demonstrate a strong attractiveness of the team, and a genuine ability to develop international collaborations.

Assessment of the unit's interaction with the social, economic and cultural environment

Team 1 is involved in the creation and direction of an Institute for Ageing (Montpellier) and participates in the "Semaine du Cerveau" public event, showing the wish to spread knowledge on brain to uninitiated people. Moreover, 2 members of the team have an international patent.

Assessment of the unit's organisation and life

Team 1 regularly takes part in meetings involving all the teams of the unit, which aim at enhancing collaborations between researchers of MNDN. Each month, MMDN welcomes scientists from other groups. There is a strong willingness to develop scientific exchanges between members of the team and other groups.

Assessment of the unit's involvement in training through research

During the last five-year contract, the team had a strong involvement in educational programs and research training: 6 PhD students, 22 master students.

Assessment of the strategy and the five-year plan

This new project is the logical continuation of previous works on MIM (Microcebus murinus). The aim is to develop non primate models of AD (Alzheimer disease), PD (Parkinson disease) and prion diseases, and to understand molecular basis of such diseases.

These models are of strong usefulness to test new candidates for the treatment of these pathologies.

The global strategy presented by team 1 is ambitious and the project is relevant with regards to the expertise and skills of the members. New techniques, such as those aiming to work out tests to measure cognitive and motor deficits, are developed through an appropriate collaboration with team 2. This is an example, among several others, which shows the translational policy within MMDN. The ambition of this team is to be considered as a reference center for the use of MIM and they take steps to achieve this goal by establishing a biobank open to the scientific community, which leads to national and international collaborations, and should result in related publications.

Conclusion

- **Strengths and opportunities:**

– the team is a reference center for the use of MIM;

– there are numerous collaborations;

– attractiveness for researchers and students is obvious.

- **Weaknesses and threats:**

– there is a lack of collaboration with physicians and clinicians working on neurodegenerative pathologies; such collaborations could lead to a complete bed-to-bench approach;

– there could be a risk for multifocal and disseminated research activities, ranging from zebrafish to lemurs, Parkinson's to Alzheimer's diseases, and maintenance and screening of a primate colony for gene transfer.

- **Recommendations:**

Try to keep focused. There is no other particular recommendation worth mentioning.

Team 2: Endogenous Neuroprotection in Neurodegenerative Diseases

Name of team leader: Mr Tangui MAURICE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1 (Post-doc) + 1 (Visitor)	
N6: Other contractual staff (without research duties)		3
TOTAL N1 to N6	**6**	**7**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	3

• Detailed assessments

Assessment of scientific quality and outputs

One characteristic of the work of this team is the development, during many years, of an acute Alzheimer model obtained by intracerebral injection of $A\beta_{25-35}$. This international expertise allowed the identification and validation of original pharmacological targets in Alzheimer's disease (AD):

- the σ1 agonists as neuroprotectants in AD, which indisputably constitutes a real strength of this team;

- the role of PLTP (phospholipid transfer protein) as a protective factor in AD;

- the role of DYRK1A in AD pathology and the interest of a treatment by DYRK1A inhibitors (through the Pharmasea collaborative project).

All these works were and will be completed in different and relevant transgenic models of AD or transfected cells, which are now major tools in preclinical pharmacology. Concerning this subject, this team established new double-transgenic mouse lines, such as APPm /σ1 KO and APPm/PLTP KO, demonstrating a real expertise in this area.

All this investment in pre-clinical assessment of drug candidates was rewarded by 2 patents. In addition, one molecule, the mixed σ1/muscarinic ligand ANAVEX2-73, was shown to be neuroprotective in AD models *in vivo*, and is currently in clinical phase I/IIa.

It is important to point out that in 2009, at the instigation of team 2 leader, a Contract Research Organization (CRO) called AMYLGEN was created, with now 7 permanent employees. This start-up is supported by members of team 2 and the close links between these two groups represent a real added value for team 2.

During the last 5-year period, members of team 2 wrote 58 papers (with a mean impact factor of 4.7) and presented 15 oral communications and 59 posters in national and international congresses. Some articles were published in high-profile journals, with high impact factors such as: Trends Pharmacol (9.3), Neuropsychopharmacology (8.0) or Neurobiol Aging (6.2). The review article published by the team leader on ¤1 receptors has attracted 135 citations in less than 4 years.

Altogether, this constitutes a very good output, taking into account the fact that this result was obtained with 6 permanent members.

Assessment of the unit's academic reputation and appeal

The members of this team are involved in different national (Pharmasea collaborative framework; LipStick LABEX) and international projects, in particular in exchange programs. Furthermore, team 2 welcomed researchers from India or Cuba. This accounts for an important attractiveness.

The work performed by this team has a worldwide reputation, since the members of the teams were invited 11 times at international meetings and 9 times in foreign universities or companies.

The members of this team are involved in numerous expertise-related work: more than 120 articles, 7 reviewed grant applications, as well as committees for PhDs (6 thesis defenses) and HDR (2 defenses).

Assessment of the unit's interaction with the social, economic and cultural environment

Several industrial contracts were established between team 2 and different firms in France (ManRos therapeutics, CLL Pharma) or societies in Germany, USA and Russia.

As mentioned above, an interaction is very strong with AMYLGEN (7 employees), and team 2 had an active participation in the creation in 2009, and the development since then of this start-up. The leader of team 2 belongs to the scientific advisory board of AMYLGEN. This point demonstrates the dynamism of the team.

Team 2 is also involved in the animation of the CompAn behavioral phenotyping platform, a technical service for phenotyping mouse and rat models. 8 publications originated from this strong collaboration.

Moreover, this team is involved in the annual Surgery School of Biocampus Montpellier to obtain the authorization to perform surgical experiments.

Assessment of the unit's organization and life

Team 2 regularly contributes to meetings involving all the teams of the unit, what should help to enhance inter-team collaborations within MMDN. Each month, MMDN invites scientists from other groups to develop scientific exchanges between members of the team and other groups.

Assessment of the unit's involvement in training through research

The team has a good involvement in educational programs and research training: 6 PhD students, 4 Master 2nd year and many other students for a shorter training period. The members, including full-time researchers, are involved in licenses and master lectures. It's not always the case in many french institutional research teams.

Assessment of the strategy and the five-year plan

A part of the new project is in continuity with previous work developed during the last 5-year period: for example, after the development of original AD transgenic mice models, the members of team 2 plan to analyze at biochemical and behavioral levels:

- APPm/PLTP KO mice generated to study the effect of PLTP in AD;
- APPm/sigma1KO mice developed to study the role of sigma1 chaperone protein in AD.

And they will continue to explore innovative pharmacological strategies (targeting PLTP or by maintaining a partnership with the firm ANAVEX LIFE SCIENCES) to assess the biochemical mechanisms of molecules acting as mixed muscarinic M1 receptors and sigma 1 ligands.

In addition, new projects have been/will be developed such as to investigate the effects of A¤ on neuronal DNA damages and cell cycle re-entry.

The scientific project is relevant with regards to the expertise and skills of team 2 members. It addresses important issues in the domain of toxicity of beta-amyloid and treatment of AD, which represents a crucial challenge with the increasing problem of this pathology in public health.

Conclusion

The group is well funded and internationally recognized and has a clear vision for going forward with the work that they want to do. They are well-positioned to conduct their work program. The results should bring valuable data for the understanding of A¤ toxicity and innovative therapeutic options for the treatment of AD.

- **Strengths and opportunities:**

- start-up Amylgen;
- strong and lasting collaboration with Pharmaceutical companies;
- real attractiveness for researchers and students.

- **Weaknesses and threats:**

- lack of collaboration with physicians and clinicians working on AD;
- a permanent technician/engineer is missing (by comparison with other teams of the research unit).

- **Recommendations:**

Recruit a full-time, permanent technician/engineer in a reasonable delay.

Team 3: New Molecular Interactions in Proteoinopathies

Name of team leader: Ms Mireille ROSSEL and Ms Véronique PERRIER

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	3	4
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)	2	2
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**8**	**7**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs

Team 3 “New molecular interactions in proteinopathies” was created in January 2011 after the last AERES evaluation and got a global ranking of A. The main objectives of the team are (I) to understand the early mechanisms involved in neurodegenerative diseases and (II) to define new diagnostic and therapeuthic strategies. In the 2,5 years of activities, they have particularly focussed on two proteins involved in developmental processes and neurodegenerative diseases: PrP and Reg-1α.

First, they have developed new experimental methods to assess how pressure and temperature jumps affect the protein folding and aggregation, and the formation of amyloid fibrils. They showed that high pressure permitted to switch between pathways leading to spherical particules to amyloid fibrils and back to soluble protein.

These results were published in several peer-reviewed journals in the form of 5 papers since 2011 (journals are: J Biol Chem, J Neurosci, Curr Top Med Chem, Int J Cell Biol, Neuropsychopharmacology).

Second, they have identified compounds that interact with prions, induce their oligomerization and decrease the infectivity. This allowed them to develop an important diagnostic tool, the "Rapid Centrifugation Assay" applicable to human samples. Diagnosis of blood samples are currently being developed. This gave rise to a high-impact publication in 2011 and a patent (PCT/IB2008/055465, 19 Dec 2008, international extension in 2011). The supporting data were largely presented through seminars and posters.

Third, they have developed a lentiviral-based gene therapy protocol targeting the late stage of the prion disease. The results were also published and presented at international meetings in 2008.

Finally the team has 2 publications in preparation on the role of Reg-1α as a neurotrophic factor and as a differentiating factor in neural stem cells. In addition, the team has developed a zebrafish facility in the past 2 years that is now operational. Team 3 is now using this model to complement the study of the roles of PrP and Reg-1α.

Given that (I) the team has been newly created in 2011, (II) half of the team, including one of the two heads, joined the lab only at that time point and (III) they successfully established a fish facility which requires a significant amount of time and effort, the experts committee has estimated it was not possible to objectively grade this team for its own work yet. The committee wants nevertheless to point out that, despite these facts, the scientific output of this new team is already very satisfactory and promising and the research project is both competitive and sound.

Assessment of the unit's academic reputation and appeal

For the reasons mentioned above, the AERES committee found difficult to evaluate these items too.

Nevertheless, the experts committee wants to point out that team 3 has attracted third-party funding from a diversity of funding bodies in the past 2,5 years including a "Région LR chercheur d'avenir" grant to Ms Véronique PERRIER, several EPHE grants to Ms Mireille ROSSEL and Ms Anne MARCILHAC as well as private fundings. Together with a high number of publications in peer-reviewed journals (see above) and a very high number of oral communications and posters at both national and international meetings, this largely ensures to the team an excellent level of visibility at both national and international levels.

This is also illustrated by an impressive number of guest scientists (from Spain, Greece, Czech Republic and Germany) that have spent between 1 week and 8 months with the team since 2011.

Their large involvement in teaching and vulgarization (see below) also largely contributes to their local reputation.

Finally the team manages to attract a good number of PhD students and postdocs. Currently 2 postdoc are present in the team, apparently funded by the team.

Assessment of the unit's interaction with the social, economic and cultural environment

For the reasons mentioned above, the AERES committee estimated it was not possible to evaluate this too new team.

Nevertheless, the experts committee wants to point out that team 3 is extremely active in social and cultural events, as illustrated by an impressive number of vulgarization articles and lectures on ageing. Importantly, the institute of ageing whose goal is to improve the dissemination of knowledge on ageing was funded by the french research ministry at the initiative of members of team 3. And, very interestingly, they have initiated a training program for guiding and assisting elderly person (2-years education after baccalaureat).

Last but not least, they have published a patent on the "RCA" method to identify the presence of the prion protein in tissues

Assessment of the unit's organization and life

Members of team 3 meet on a weekly basis in lab meetings and actively participate to the bi-weekly unit reunion. They have also a monthly journal club.

Assessment of the unit's involvement in training through research

Team 3 is largely involved in teaching with currently 3 EPHE faculty. They are responsible of a number of EPHE modules as well as for continuing education.

Team 3 has been very active with 6 PhD thesis defended between 2009 and 2012. Except one, all students defended with at least 1 good to very good 1st author paper, sometimes more and each student had presented 2 to 4 posters at the occasion of scientific meetings. Two of them also participated to the writing of a book chapter.

Assessment of the strategy and the five-year plan

Team 3 proposes to pursue 2 different directions in the next 5 years. The first one is the further development of the RCA method to establish a screening of PrP on blood samples. This is of course a very promising approach with high medical relevance (and potential impact). The second one is to continue with the dissection of the role of Reg1α in the physiopathology of tauopathies. For this purpose they propose to combine cell culture, zebrafish and mice to analyze the cellular interactions and functional link between Reg1 α and Tau on the one side, and Reg1 α and PrP on the other side, and establish the role of reg1a for aggregation and neurotoxicity. Preliminary results already exist and the combined approaches with 3 different models should allow the team to obtain additional interesting and publishable results rapidly.

In a longer term approach, the team aims at studying the effects of metabolic (diabete, inflammation) and environmental (pesticides) risk factors in the physiopathology of neurodegenerative disorders. They will do so in relation with Reg1α, Tau and PrP. For this purpose, they will expose different murine and zebrafish models of neurodegenerative diseases to pesticides in order to determine if this can trigger or increase the disorders. The team has already preliminary data on this project showing that a herbicide is triggering the oligomerization of the prion protein. The combinatorial approach they now want to take is promising. Furthermore, the project will be developed in the context of the JPND consortium, which is coordinated by one of the PIs.

Finally, in a more global, collaborative and multidisciplinary approach, team 3 wants to connect different aspects of the AD/Tau pathology with perturbation of environmental factors such as glucose metabolism and systemic inflammation. This will be done using human, mice, zebrafish and cell culture models in collaboration with other teams of the institute, or from abroad within networks the team is part of.

Team 3 has appropriately taken into account the recent departure of two of its members by stopping the biophysical project on protein folding and by refocusing on the molecular mechanisms of neurodegenerative diseases with 2 major topics: PrP and reg1α. These new projects are thus the logical continuation of previous works of the current members of the team. The team has also now successfully established a zebrafish facility. This new model will undoubtedly be very appropriate for many questions they want to address.

The strategy presented by team 3 is very appropriate with regards to the expertise of the members and the questions asked are timely and of high medical relevance.

Conclusion

- **Strengths and opportunities:**

- excellent scientific questions and strategy;

- very promising scientific output;

- excellent interaction with the social, economic and cultural environment;

- strong involvement in teaching and continuing education.

- **Weaknesses and threats:**

- the two members who recently left the team were extremely productive in terms of publications and largely contributed to the excellent scientific output of the team;

- the new “nucleus” has managed to develop its own independent research focus in the past 2,5 years. They have now to confirm their nice start by independently publishing high-impact papers and keep up with this high productivity.

- **Recommendations:**

- stay focused;
- appropriately combine the different animal models now available to the team to take the best out of each;
- promote and increase inter-team collaborations and publications.

Team 4: Biodemography of Vitality and Longevity

Name of team leader: Mr Jean-Marie ROBINE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1 (Post-doc)	
N6: Other contractual staff (without research duties)	3	
TOTAL N1 to N6	**6**	**2**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	1

- ## Detailed assessments

Assessment of scientific quality and outputs

This team is a very recent addition (2012) to the MMDN unit and focuses on the demography of vitality and longevity. The team leader is very well connected in his field. The team is involved in a number of projects using data that are collected on human longevity and quality of live from Europe, Japan, United States and other countries. For a number of these projects the team leader is the coordinator.

The main objective of team 4 is to understand the relationship between health and longevity. The research topics the group is involved in focus on:

- measures and limits of the human longevity;

- measures of health and quality of life among the oldest old;

- combined measures of health and longevity;

- measures and limits of the human longevity.

This topic is covered by four projects; in the M-project the group investigated alternative ways of measuring longevity that are less biased towards mortality at an infant age. A publication about a new measure has been submitted.

In a second study the group investigated age-related mortality levels in centenarians using an international database. A large study on the effects of climate on survival was performed in centenarians from 47 prefectures throughout Japan, and a study on sex and longevity was performed on available data from Europe between 1998 and 2003.

- **Measures of health and quality of life among the oldest old.**

This topic is covered by two projects:

- for the first project (Five Country Oldest Old Project (COOP), data on health status of centenarians from five countries have been collected in 2013. Data analysis will start in 2014;

- the second project (European challenge for healthy ageing and Genetics of Healthy Aging; collaborative project) the group is involved in data analysis and this will be a very good data resource for the coming years.

- **Combined measures of health and longevity.**

Joint Action European Health and Life Expectancy Information System. The EU centered study monitors the Healthy Life Years (HLY) in EU members states to analyze for example trends, patterns and differences in HLY in the EU. The study will provide information to policy makers to help reach the EU goals of increasing HLY by 2 years by 2020.

Overall the studies investigate very important demographic aspects of our ageing population and the results are either published in relevant and high impact journals such as Lancet (N=2), Nature Communication, J Clin Epidemiol, etc), or they provide tools for policy makers to reach strategic goals.

The team leader is a major participant and PI in most of these studies that are very internationally-oriented and provide important demographic data for our population.

Assessment of the unit's academic reputation and appeal

The fact that the members and more specifically the team leader, are coordinating a series of international studies that are published in high ranking journals and/or are supported by the EU and are being used by policy makers, indicates the importance and high quality of the work. The current reputation of the groups is largely based on the PI and the plan for the development of the group, including for the period after the retirement of the PI in a few years, needs to be clarified in order for the team to remain appealing in the coming years.

Assessment of the unit's interaction with the social, economic and cultural environment

The team interacts with the scientific community by the publication of regular research papers, with policy makers by generating reports and in addition with the general public by items in television. This seems appropriate to the goals of the team but this type of research would be suitable for a more intensive interaction with the environment.

Assessment of the unit's organization and life

There is information on the general organization of the overall unit where it is stated that each team regularly contributes to meetings involving all the teams of the unit, what helps to enhance collaboration between teams of MMDN. Each month, MMDN invites scientists from other groups to develop scientific exchanges between members of the team and other groups.

Assessment of the unit's involvement in training through research

There was no specific mention of training through research for this team specifically apart from mentioning that PhDs and postdocs are welcome and the fact that they have employed a Master student. It does not seem that the team is very actively involved in training.

Assessment of the strategy and the five-year plan

Team 4 has been very successful in the past years and they aim to continue their work in the coming years. A number of project are ongoing and it is expected that the group will remain as productive as they have been in the past years. This part of the five-year plan, namely the one that focused exclusively on epidemiological approaches of aging in human populations, is excellent.

Unfortunately the second aspect of the future plan (i.e., the application of epidemiological tools used in humans to other animal species used in the MMDN research unit) has not been worked out very well and this also touches on another important aspect for this team; How can their research activities be connected to those of the other teams to create synergy ? The work of team 4 is very much centered on that of the team leader and there seems to be very little connection to the work of the other teams. What is the added value for MMDN to have the team leader on site as he could carry out his work everywhere ?

There is a very general description of a collaborative project with the other teams to study longevity not just in humans but also in the other model organisms available at the center. The exact content and approaches of this project are however unclear.

Conclusion

The group is well funded and internationally recognized. They have a clear vision for going forward with the work that they want to do. They are well positioned to conduct their work program. The results should bring valuable data for our understanding of the demographics of (healthy) aging.

- **Strengths and opportunities:**

- very well connected internationally;
- well-funded;
- high Level research.

- **Weaknesses and threats:**

- lack of connectivity with the other teams at MMDN;
- low involvement in training through research.

- **Recommendation:**

Do all possible efforts to connect research with that of other teams using ageing models that could be analyzed with the investigation tools used in humans (should be feasible in at least mice and zebrafish, and why not in microcebus).

Team 5: Huntington's disease: Neurophysiopathology from *Drosophila* to Mice

Name of team leader: Ms Florence MASCHAT

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions		1
N3: Other permanent staff (without research duties)		1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6		**3**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

Team 5 on *"Huntington's Disease: Neurophysiopathology from drosophila to mice"* is a new team that will join MMDN in 2014. The main objectives of this team were (1) to determine the role of the homeoprotein Engrailed during neurogenesis and (2) to identify protective factors against neurodegeneration in Huntington's disease. Both studies were addressed mainly using Drosophila as a model system.

In a first set of studies, they demonstrated that Engrailed interacts physically and genetically with Gooseberry-Neuro to build up the posterior commissure, which shapes the ventral nerve cord in fly. Thereafter, they combined microarray and chip-on-chip approaches to identify common targets involved in the formation of posterior commissure. The former results gave rise to one peer-reviewed publication (Plos ONE) and the latter, to a manuscript in preparation.

From the above study, they postulated that Engrailed could be secreted from glial cell to instruct the formation of posterior commissure. They tackled this question in a second study, by providing the first evidence that Engrailed is secreted in Drosophila, and by demonstrating that secreted Engrailed acts as a signaling molecule in wing development. These nice data gave rise to a high-impact publication in 2011 (development), and were presented through seminars and posters.

In a third set of studies, they provided evidence that the fly ortholog of Huntingtin is regulated by Engrailed. Moreover, they demonstrated that fly and human Huntingtin have a protective role on mutant Huntingtin toxicity, confirming in fly earlier results observed in mouse by others. Most interestingly, they identified a short 23-aminoacid peptide (p42) in Huntingtin that is sufficent to inhibit mutant Huntingtin toxicity in fly as well as in mammalian cells. These results were disseminated in 2 peer-reviewed journals in 2008 (high-impact) (Human Molecular Genetics) and 2013 (Plos ONE), in several oral presentations and posters, and led to a patent. Finally, the team is now developing the p42-peptide for therapy and has promising preclinical assessment in mouse and fly, which is the object of a submitted paper.

In conclusion, the team has reinforced relatively new concepts, such as the role of homeoprotein secretion in development or the importance of Huntingtin loss of function in the pathogenesis of Huntingtons' disease. They provided novelties on the role of Engrailed on the posterior commissure formation and the discovery of the protective p42 may have high medical importance. Taking into account that the team size seems to have been relatively small over the past 5 years, the originality of the work and the scientific production is very satisfactory and promising. However, given that the team joined the lab a couple of months ago, the experts committee has estimated it was not possible to further evaluate this team within this lab yet.

Assessment of the unit's academic reputation and appeal

Its international visibility relies majorly on publications in 3 high impact journals (IP>6). The PI was also invited to give seminars in several institutes and participated to several national and international meetings. The PI was requested as reviewers by several high impact journals and international funding bodies as well as for academic evaluation of PhD thesis and HDR. Another team member is part of CNRS commission.

The PI mentored 3 PhD, 3 post-doct, and several masters over this period, and was able to establish fruitful collaborations with excellent national and international research groups to carry out his projects. The PI is organizing yearly Montpellier fly meeting.

The reputation of the team is mainly corroborated by the funding the PI received from several funding bodies: UM2, CNRS soutien au transfert and ANR émergence, the most recent one. However, due to the reasons mentioned above, the experts committee has not marked this team for its scientific reputation and appeal.

Assessment of the unit's interaction with the social, economic and cultural environment

The PI holds a patent and is currently collaborating with a biotech to use new technology for drug delivery, with the perspective of patent consolidation or licensing. The PI was involved in a local cultural event. Taking into account that the team size seems to have been relatively small over the past 5 years, the interactions are satisfactory. However, due to the reasons mentioned above, the experts committee has not marked this team for these activities.

Assessment of the unit's organisation and life

Does not apply for this team.

Assessment of the unit's involvement in training through research

The PI mentored 3 PhD, 3 post-docs, and several masters over this period. Two PhD students defended with 1-2 very good publications. The PI participated to Master teaching. Taking into account that the team size seems to have been relatively small over the past 5 years, its involvement in training through research is highly satisfactory. However, due to the reasons mentioned above, the experts committee has not marked this team for these activities.

Assessment of the strategy and the five-year plan

The team proposes to entirely focus on the physiological role of huntingtin and endogenous p42-like fragment, and on the development of P42-based therapy. They decided to drop their research program on Engrailed, which is a very appropriate decision to avoid scattering and to better investigate interactions with the unit's teams.

First they have preliminary data indicating that Huntingtin behaves as a MAP and is proteolyzed to generate one heavy and one p42-like fragments. They want 1) to identify the proteolytic site, 2) to study the physiological role of the p42 peptide in the proteolytic process and in the stabilization of microtubule by Huntingtin. This is of course very interesting as it may unveil a new function of Huntingtin and a protective mechanism of p42 peptide.

Second, the team has a full program to develop a P42-based therapy using diverse strategies to optimize the delivery and uptake of p42 peptide and to enhance its protective effect, notably by fusion with degradation-addressing sequences or by developing a combinatorial therapy. They also want to determine the protective mechanisms of p42. To do so, they are developing a more multidisciplinary approach, by shifting from fly to mouse model, by using cutting-edge technologies (proteomic, Aonys) and by taking advantage of the unit's expertise in viral vector delivery into CNS. In summary, the p42-based therapy project is original and largely differs from current therapies being under development for Huntington's disease. The approach is thoughtfully designed.

Conclusion

- **Strengths and opportunities:**

- excellent scientific questions, expertise and methodologies;

- very good scientific output and interaction with economic, social and cultural environment.

- **Weaknesses and threats:**

The research on Huntingtin as a MAP is very interesting, but relies on preliminary data that the experts committee has not seen and was unable to assess.

- **Recommendations:**

- develop synergy with the research unit to strengthen some ongoing projects;

- develop the research project taking into account the use of model systems where full length mutant huntingtin is expressed;

- increase visibility and network participation.

5 • Conduct of the visit

Visit dates:

Start: January 31th 2014 at 09.00 am

End: January 31th 2014 at 06.40 pm

Visit site: GENOPOLYS

Institution: Campus Arnaud de Villeneuve
141 rue de la Cardonille
34396 Montpellier cedex 5

Specific premises visited:

Due to time and space constraints, the experts committee did not visit any of the unit's facilities.

Conduct or program of visit:

The visit started with a closed-door meeting of the experts committee, then with an overall presentation by the head of the unit project and a discussion. This was followed by a presentation of each team leader and a short discussion with each of them. After lunch, the experts committee met with representatives of the EPHE, Université de Montpellier and the INSERM, then with representatives of the two doctoral schools to which PhD students hosted by the unit were affiliated (EPHE and Université de Montpellier). Subsequently, two parallel meetings enabled half the experts committee to spent time with the PhD students and post-docs, the other half having met the technical staff of the unit for approximately the same duration. Then, the entire experts committee had a discussion with the researchers of the unit, whatever their affiliation (CNRS, EPHE, INSERM University). Followed a discussion between the experts committee and the head of the unit project, and finally a closed-door meeting during which the experts committee discussed all points of the day, which were not numerous, and agreed about the various requested evaluations as requested by the AERES; be they for the unit in general or for each of the 5 teams, these were all consensual. There was no return given to the head of the unit project after the visit was over. The experts committee would like to emphasize an excellent and very professional welcome.

Program of the experts committee AERES

Molecular Mechanisms in Neurodegenerative Diseases (UMR_S 710, NUM, EPHE ,INSERM*)*

January 31th 2014

Actual director: Mr Jean-Michel VERDIER
Proposed director: Mr Jean-Michel VERDIER

AERES Scientific Delegate (DS): Mr Yves TROTTER

Scientific committee:

Chair: Mr Jean-Christophe CASSEL (France)

Members: Mr Jean-Michel GAILLARD (France), Ms Virginie LECAUDEY (France), Mr Bernard FAUCONNEAU (France), Mr Peter HEUTINK (Germany), Mr Yvon TROTTIER (France)

Experts Representative of the institutions: Mr Damien GALANAUD (INSERM CSS 8), Mr Jerôme TROUSLARD (CNU 69)

Representative of ITA: Ms Hélène GROS-DAGNAC (INSERM CSS8)

08.45 am	Welcome breakfast
09.00 am	Door-closed meeting: presentation of AERES to the experts committee by the DS
09.20 am	Presentation of the experts committee and presentation of AERES to the unit by the DS
09.30-10.15 am	Director of the unit (presentation + discussion): presentation of the past activities and project (Mr Jean-Michel VERDIER)

Team presentations (including discussion)

10.00 am	Scientific assessment and projects: team1 "Cerebral Ageing & Neurodegenerative Diseases" (Ms Nadine MESTRE-FRANCÉS)
10.45 am	Coffee break
11.00 am	Scientific assessment and projects: team 3 "New Molecular Interactions in Proteinopathies" (Ms Mireille ROSSEL & Ms Véronique PERRIER)
11.30 am	Scientific assessment and projects: team 2 "Endogenous Neuroprotection in Neurodegenerative Diseases" (Mr Tangui MAURICE)
12.00 pm	Scientific assessment* and projects: team 5 "Huntington's Disease: Neurophysiopathology from Drosophila to Mice" (Ms Florence MASCHAT) (*scientific assessment not included into the MMDN's asessment)
12.30 pm	Scientific assessment and projects: team 4 "Biodemography of longevity and vitality" (Mr Jean-Marie ROBINE)
01.00 pm	Lunch with all laboratory staff
02.00 pm	Meeting with the representatives of the institutions *Audience: members of the experts committee and DS*
02.45 pm	Meeting with permanent and non-permanent staff: - meeting with the technical staff *Audience: members of the experts committee, DS and ITA representatives of the organisms* - meeting with PhD students and Post-docs and/or fixed-term contract researcher, engineers *Audience: members of the experts committee and DS* - meeting with researchers, professors and assistant professors *Audience: members of the experts committee and DS*
03.30 pm	Meeting with the representative of the « École Doctorale »: Mr Philip HUYSE (director of the ED n° 472 EPHE) and Mr Michel DESARMENIEN (director of the ED CBS2) *Audience: members of the experts committee and DS*
03.45 pm	Break
04.00 pm	Discussion with the head of the unit *Audience: members of the experts committee and DS*
04.30-06.00 pm	Door closed meeting *Audience: members of the experts committee and DS*

Specific points to be mentioned:

Mr Jean-Michel GAILLARD was not present during the site visit.

6 • Supervising bodies general comments

nouvelle université de Montpellier
un projet, une ambition

UNIVERSITÉ MONTPELLIER 2
SCIENCES ET TECHNIQUES

Le Président

Montpellier, le 3 avril 2014

M. Didier HOUSSIN
Président de l'AERES

M. Pierre GLAUDES
Directeur de la section des unités de recherche

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75002 Paris

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Affaire suivie par :
Ingrid CHANEFO,
Directrice de la Recherche et des Etudes Doctorales

Objet : Réponse de l'établissement support au rapport d'évaluation de l'unité MMDN – UMR_S 710
Réf. : rapport d'évaluation S2PUR150008344

Messieurs,

Je tiens à remercier le comité de visite pour la qualité de son rapport d'évaluation concernant l'unité de recherche MMDN – Mécanismes Moléculaires dans les Démences Neurodégénératives (UMR_S 710), dirigée par Monsieur Jean-Michel VERDIER.

J'ai bien noté les remarques formulées par le comité de visite.

En tant que tutelle universitaire de cette unité de recherche, je ne formulerai aucune remarque supplémentaire

Je vous prie d'agréer, Messieurs, l'expression de mes salutations les plus respectueuses.

Pour le Président et par délégation,
Le Président de l'Université Montpellier 2,

Michel BERNARDELLE
Vice-président du Conseil Scientifique

UNIVERSITÉ MONTPELLIER 2 SCIENCES ET TECHNIQUES

Pièce(s) jointe(s) :
Relevé des erreurs factuelles à rectifier dans le texte du rapport
Observations générales formulées par le directeur

Unité de recherche U710
Mixte avec l'Université Montpellier 2 et l'EPHE
Mécanismes moléculaires dans les démences neurodégénératives
Jean–Michel Verdier, Directeur

March, 28, 2014

Reply to the AERES Visiting Committee (31st of January 2014)

On behalf of the MMDN's personnel, I would like to thank the AERES committee for the time and effort they gave to our review, and especially for the in-depth analysis of all items (research, teaching, attractiveness, economical development, and dissemination). The rich content of conclusions will be of major help for the future.

We are very pleased that the overall evaluation was very positive both for the lab and for all teams. We also appreciated the comments for improving our project.

We take note of pertinent comments on aspects that we shall maintain (national and international competitiveness, collaborative networks with industry, focus on a limited number of projects, originality of the research, interaction with social, economic and cultural environment, high quality of publications) or improve (relationships with medical teams in Montpellier, increase of inter-team collaborations, team 4 and 5 building). This latter point is discussed hereafter.

We have established connections with the neurology department of the hospital with the arrival of a neurologist doing a PhD thesis in team 5. We think that this first close connection should allow us to increase our partnership with the hospital in the near future.

Regarding inter-team collaborations, the emergence of teams other than 1 and 2, is very recent (2011, 2012, and 2014). This fact has to be taken into account although we have already published common papers. Furthermore, this item should not be considered only in terms of publications. A lot of discussions, exchanges either unformal or during seminars are permanent and stimulate future collaborations.

We agree with the observation that in regards with all our projects, our animal facility capacity is limited. We are examining several options to increase the available space within the campus, or within facilities in other institutes in Montpellier.

An effort will also be made to better balance the technician supports in each team. So far, order of priority has been established for common services and animal breeding, but we will follow the committee suggestion to try to provide at least one full-time technician per team.

In terms of Team 4 building, since the AERES visit, we have recruited a senior researcher with a permanent position, specialized on ageing studies, which will join Team 4 in december 2014, once the mobility has been acted by his administration. In addition, one Asssitant Professor position will be asked to EPHE for Team 4 for developing new mathematical models in epidemiological studies of ageing. The reinforcement of Team 5 will also be considered, but will depend on how the project grows in scope over the years.

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