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

Department for the evaluation of research units

AERES report on unit:

Neurodegenerative Disease Laboratory

LMN

Under the supervision of the following institutions and research bodies:

Commissariat à l'Énergie Atomique et aux Énergies Alternatives - CEA

Centre National de la Recherche Scientifique – CNRS

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

Université Paris-Sud

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. Abdelhamid BENAZZOUZ, 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:	Neurodegenerative Disease Laboratory
Unit acronym:	LMN
Label requested:	CEA-CNRS
Present no.:	URA 2210
Name of Director (2013-2014):	Mr Emmanuel BROUILLET
Name of Project Leader (2015-2019):	Mr Emmanuel BROUILLET

Expert committee members

Chair:

Mr Abdelhamid BENAZZOUZ, Institut des Maladies Neurodégénératives, Université Bordeaux Segalen

Experts:

Ms Jocelyne CABOCHE, Université Pierre et Marie Curie, Paris

Mr Mohamed JABER, Université de Poitiers (representative of CSS INSERM)

Mr Guy MENSAH-NYAGAN, Université de Strasbourg (representative of CNU)

Mr Nicola PAVESE, Neurology Imaging Unit, Imperial College London, United Kingdom

Mr Klaus PETRY, Université Bordeaux Segalen (representative of CoCNRS)

Ms Nicola SIBSON, University of Oxford, United Kingdom

Scientific delegate representing the AERES:

Mr Yves TROTTER

Representatives of the unit's supervising institutions and bodies:

Mr Gilles BLOCH, CEA

Ms Brigitte RENE, INSB-CNRS

Mr Etienne HIRSCH, ITMO Neuroscience

Mr Michael SCHUMACHER (representative of the Doctoral school n°419)

1 • Introduction

History and geographical location of the unit

The CEA-CNRS URA 2210 unit (CEA unit associated to CNRS) is located at MIRCen (Molecular Imaging Research Centre, Fontenay aux roses), a Service of the Biomedical Imaging Institute (I²BM) of the CEA. URA 2210 also depends on CNRS (commission 28, INSB).

The URA 2210 is the continuation of the URA CEA-CNRS 1285 originally created and directed by Mr André SYROTA at the Service Hospitalier Frédéric Joliot (SHFJ, CEA, Orsay) as an interface between cellular and molecular neurobiology and brain imaging. The URA 2210 unit was created in 2004 with Mr Philippe HANTRAYE as its director. In 2011, the URA 2210 was renewed after its first AERES evaluation with Mr Emmanuel BROUILLET as its director.

At the beginning of 2009, the majority of the members of the URA 2210 unit moved to MIRCen, a Preclinical Research Centre jointly financed and built by CEA and INSERM (CRC CEA-INSERM) at Fontenay-aux-Roses. At this time, all preclinical research activities of the URA 2210 were concentrated in MIRCen whereas the clinical activities of the unit remained located at Henri Mondor Hospital and at SHFJ for the PET/MRI imaging of the patients.

In addition to its affiliation to CNRS and CEA, URA 2210 asks for its affiliation to Paris 11 (Université Paris-Saclay in 2015) in order to contractually reinforce its long standing links with this south Paris University.

Because the research activities of URA 2210 are clearly oriented towards medical applications, the URA 2210 also asks for its affiliation to INSERM.

Management team

The (URA 2210) neurodegenerative disease laboratory is headed by Mr Emmanuel BROUILLET (Research director at CNRS) since 2010. He will be the director of the unit for the next five years.

The lab is constituted of 3 research teams. Team 1 which focuses its research on the role of "Cell-cell interactions in neurodegeneration" is directed by Mr Gilles BONVENTO (Research director at Inserm). Team 2 which focuses its research on "Preclinical and clinical therapeutics for neurodegenerative diseases", is directed by Mr Philippe HANTRAYE (Research director at CNRS). Team 3, is focused on "Multimodal imaging of neurodegenerative diseases", and is directed by Mr Marc DHENAIN (Research Director at CNRS).

Unit workforce

Unit workforce	**Number as at 30/06/2013**	**Number as at 01/01/2015**
N1: Permanent professors and similar positions	1	1
N2: Permanent researchers from Institutions and similar positions	12	12
N3: Other permanent staff (without research duties)	16	17
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	1
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	5	4
N6: Other contractual staff (without research duties)	6	4
TOTAL N1 to N6	**41**	**39**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	7	
Theses defended	12	
Postdoctoral students having spent at least 12 months in the unit*	11	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	5	7

2 • Assessment of the unit

Strengths and opportunities related to the context

The URA 2210 is internationally acknowledged as a unit using translational approaches from basic science to clinical applications in the field of neurodegenerative diseases including Parkinson's, Huntington's and Alzheimer's diseases. The strength of the unit relies on its unique gathering of scientists experts in different fields using multidisciplinary methodologies. Members of the unit are experts in:

- the development of methodologies such as gene transfer, image processing, PET (Positron Emission Tomography), MRI (Magnetic Resonance Imaging), and NMR (Nuclear Magnetic Resonance spectroscopy) brain imaging;

- the development of animal models using gene transfer in rodent and non-human primates, which contributes to better understanding the pathophysiology of disease progression. The unit is organized in such way that scientific equipments are accessible to all the teams. These include MIRCen platforms (brain imaging, image processing, vectorology, behaviour and histology). The URA 2210 is hosted at MIRCen and several technicians and engineers of the unit are part-time dedicated to platform activities. The clinical group has access to brain imaging PET facilities at Service Hospitalier Frédéric Joliot (CEA). These platforms are also dedicated to national and international collaborations.

Members of the unit have developed very strong relationship with pharma industry (IPSEN-BEAUFOUR, OXFORD BIOMEDICA, SANOFI-AVENTIS, SERVIER, ROCHE, ELI LILLY, etc).

Scientists gather their expertise in taskforces to synergistically work on transversal programs. The unit members are involved in clinical trials in collaboration with clinicians at Henri Mondor Hospital (Creteil).

Weaknesses and threats related to the context

Disequilibrium in the size of the teams, including the technical staff, and the small size of one team makes the feasibility of the projects vulnerable.

A lack of focus in overall direction and broad range of some projects that merit a more in-depth attention. The coherence of overall goals is not clear for some projects.

The experts committee noted that the lack of in depth study of mechanistic limits the teams to publish in high IF journals.

Recommendations

The teams should streamline their research plans and focus on projects with highest interest and feasibility.

It is recommended to the small team (team 3) to define a clear strategy to attract new researchers.

It is recommended to encourage young researchers (in particular in team 2) to lead some of the team's projects.

3 • Detailed assessments

Assessment of scientific quality and outputs

The teams of URA 2210 unit have focused their research on neurodegenerative diseases, especially Huntington's, Parkinson's and Alzheimer's diseases. They developed a translational research strategy allowing the transfer of findings from basic research in animal models of these diseases to clinical trials in patients. They developed animal models using lentiviral and AAVs vectors mimicking disease progression in which they developed innovative brain imaging methods to assess progression of neurodegeneration and therapeutic efficacy.

The major findings of the unit during last 5 years are:

1) the defect in energy metabolism at the level of neuron-astrocyte interactions in pathogenic mechanisms of Huntington's disease;

2) the efficacy of gene transfer using siRNA for the treatment of Huntington's disease;

3) the efficacy of gene transfer using viral vectors targeting the replacement of dopamine in MPTP-treated non-human primate. This approach was successfully transferred to parkinsonian patients (The Lancet paper);

4) the realization of new animal (rodent and non-human primate) models of Alzheimer's disease;

5) the development of innovative brain imaging methods.

Given the medium size of the unit, the scientific output is of excellent quality. The unit has published more than 110 papers in peer-reviewed journals since 2008. Among the most important papers that were led by researchers from the unit (as first and/or last author) are:

- Sci. Translational Med (2009);

- PNAS (2009);

- Ann Neurology (2009);

- Human Molecular Genetics (2008, 2010x2, 2013x2);

- Journal of Neuroscience (2009, 2011, 2012x2);

- Neuroimage (2008, 2010x2, 2011, 2013);

- Neurobiology of Aging (2009, 2011, 2012x2, 2013x2);

- Glia (2009);

- J. Nucl Med (2009);

- J. Cereb Blood Flow Metab (2009, 2012x2);

- The Neuroscientist (2009);

- The Lancet (in collaboration, 2 members of the unit have contributed as co-authors, but not 1st/last/corresponding author).

Considering the individual achievements of each team, a discrepancy of productivity in terms of peer-reviewed publications between the teams can be noted.

In addition to the overall quality and volume of original publications, the URA 2210 members obtained three licenced patents, one for radiolabels PBR/TSPO [AD0628: EP 08291013.4 -SHFJ et MIRCen], one on siRNA strategy [AD0618: EP07290751.2 – MIRCen] and one on « silencing » specific astrocytes [AD13019: EP12305588.1. – MIRCen].

Assessment of the unit's academic reputation and appeal

Researchers of the URA 2210 are involved in a large number of national and international collaborations, as well as pharma industry partnership attesting of their excellent visibility. The fact that the lab is hosted in the MIRcen with several platforms (managed by the staff of the three teams) plays an important role in the unit's visibility.

The excellent quality of the UMR 2210 is attested by the numerous grants from public institutions, patient's foundations and pharma industry they have received. The committee noted the award of a junior ERC grant to one of the researchers and the "Grand prix de la Fondation de France & Fondation Alzheimer" to one of the team leaders.

Scientists of the URA 2210 are frequently invited to give lectures at national and international institutes and meetings.

Scientists are involved in scientific advisory boards (ANR, Dim biotherapy, Dim neurosciences, ITMO Neurosciences, ENP, JPND, NeurATRIS, etc) and editorial activities.

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

One of the most important interactions of the teams of the unit is with pharma industry (Oxford BioMedica, SANOFI, ROCHE, Servier, Eli Lilly, etc).

The team 2 leader is member of the strategic management of MEDICEN PARIS REGION.

Scientists of the URA 2210 are engaged in public activities.

Assessment of the unit's organisation and life

Because URA 2210 is hosted at MIRCen and URA 2210's researchers, engineers and technicians are deeply implicated in the running/managment of the MIRCen equipments and platforms, the teams benefit from all these equipments and platforms. The lab is organized in such a way that scientists use common resources and share facilities that allow submitting joint applications involving 2 or 3 teams. The strategy to apply to different calls is orchestrated during lab meetings to avoid internal competition and maximize chances of obtaining grants.

There are many ongoing interactions between the 3 research teams generating collaborations, which are productive. 30 % of the unit's publications include co-authors from at least two different teams of the URA 2210 unit.

The unit as a whole brings together all of the elements that are essential for the identification of novel therapeutic strategies in neurodegenerative diseases and translate these from the laboratory to the clinic.

All three teams have regular team meetings, as well as cross-cutting steering committees, in which representatives of the three teams are involved. This approach allows for a unified approach across the entire unit, and enhances the potential for inter-team collaboration.

Committee members met with the technicians and engineers of the center. They expressed their total approval of the proposed project. They have been involved in the AERES evaluation proposal. Indeed, they all have read the AERES document before it was submitted and attended the presentation preparations by the team leaders. Although many technical staff are involved in the platform activities of MIRCen (up to 50 % of their activity), all attested that they feel very well implicated in the different research projects. They are informed of the main aims to achieve and the progress of the project. They seem to interact very efficiently with researchers and PhD students, and are often associated to publications, if not to acknowledgments. Many of them have already attended scientific meetings including international ones and even had the occasion to present posters. The unit leader and the team leaders seem to have achieved a very good management of the technical staff providing them with the means to fulfil their duties in a very productive, efficient and comfortable manner.

Committee members met with PhD students and post-docs of the unit. They expressed strong enthusiasm and happiness in regard to the technical facilities (numerous skills and strong facilities offered by the platforms) notably. The unit is successful in attracting PhD students from abroad (one PhD student from Canada) and the national CEA grant application plays a key role in this attractiveness. PhD students and post-docs of the unit regularly attend national and international meetings and actively participate to local meetings.

Assessment of the unit's involvement in training through research

The URA 2210 unit is involved in training of all categories of permanent and non-permanent personnel (technicians, students, engineers/researchers). During the last 5 years 16 PhDs defended their thesis and 20 Master 2 students were trained.

The team leaders are involved in teaching and organizing courses for Paris area's Universities. Scientists are actively involved in the steering committees of different Master 2 programs and PhD programs ("École Doctorale"). The lab has an active strategy to favour the hosting of students for their Master 2 rotations and PhD training.

Assessment of the strategy and the five-year plan

During the last five years, the unit was composed of 4 teams and recently it was decided to reorganize the teams into 3 teams only according to the scientific affinities and complementarities. The candidate director is Mr Emmanuel BROUILLET.

The scientific aims of the URA 2210 for the next 5 years are envisioned in the continuity of the past and current projects focusing on three major neurodegenerative diseases (Parkinson's, Huntington's and Alzheimer's) to:

1) better understand the pathophysiological mechanisms of cell death and dysfunction;

2) develop and validate new therapeutic strategies at a preclinical stage using new rodent and non-human primate models. The researchers will evaluate novel bio-therapies based on the utilization of viral vector-based gene delivery such as CNTF (Ciliary Neurotrophic Factor), siRNA, dopamine enzyme replenishment;

3) develop and validate new brain imaging methods that could be applied for the quantitative in vivo follow-up of neurodegeneration and the evaluation of therapeutic efficacy in animal models first and then in patients.

The projects are considered important for biomedical research as they involve various complementary aspects using different techniques and approaches and many points of convergence on topics. The committee considers that the proposed projects are in general of excellent quality, and led by scientists with solid reputations and good visibility in their respective fields. However, some of the projects are too ambitious and not focused enough (See specific comments in team-by-team analysis).

4 • Team-by-team analysis

Team 1 : Cell-cell interactions in neurodegeneration

Name of team leader: Mr Gilles BONVENTO

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	5	5
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.)	2	1
N6: Other contractual staff (without research duties)	2	1
TOTAL N1 to N6	**10**	**8**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	6	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	4

• Detailed assessments

Assessment of scientific quality and outputs

Cell-cell interactions are widely recognised as an important component of many neurodegenerative diseases. However, the role of metabolism and metabolic pathways in these interactions is less clear and growing only now in importance and interest. Team 1 has identified these processes as central to Huntington's disease (HD) and plan to extend this premise to both Alzheimer's and Parkinson's disease over the next 5 years. The team employs an impressive array of state-of-the-art methods ranging from genetic screening to in vivo imaging, and span from in vitro

cell based studies to in vivo disease models and, ultimately, to man. As such, they are very well placed to undertake the proposed work, and this is innovative both in direction and approach.

The progress made over the last 5 years is excellent, as evidenced from the substantial number of publications, including several in high impact journals such as PNAS, Human Molecular Genetics, Journal of Neuroscience and Neuroimage. The team collaborates widely both nationally and internationally, in order to extend their expertise and impact.

The work of team 1 is highly interdisciplinary not least by virtue of the wide range of methodologies employed. Over the last 5 years there has clearly been some close interactions between the original team 1 (cell-cell interactions) and team 3 (in vivo imaging), and these have now been merged in the forthcoming proposal. Such interactions are no doubt facilitated by the movement of all research teams into the same location, and more recently through the introduction of combined regular group meetings.

The approaches being used within the field of neurodegenerative disease are cutting-edge and, in some cases, have not been reported elsewhere in this context. At the same time the focus on metabolic processes and in particular neuron-astrocyte interactions in the context of reactive astrogliosis, as underlying disease progression is an interesting concept that has not been widely considered previously.

Another aspect of the work from Team 1 is the focus on the development of new viral vectors, which provide both strong research tools for dissecting out causal relationships both in vitro and in vivo, and also potential new therapeutic strategies. Notably work with the CNTF-expressing lentivirus has led to a clinical trial in HD (Huntington disease) patients.

Assessment of the unit's academic reputation and appeal

Several members of Team 1 have already secured research funding from a variety of sources, including Industrial partners, which is indicative of their standing in the scientific community and their fundability. As mentioned above, they have numerous collaborations both nationally and internationally and also host a number of foreign students and postdoctoral scientists.

The high quality of the team members is attested by the numerous grants and awards they have received during the past five years. These include 1 junior ERC grant to one of the researchers within the team and 1 prestigious award “Grand prix de la Fondation de France & Fondation Alzheimer” to the team leader.

Members of the team have been involved in a number of activities at the publishing level, including acting as a Topic Editor for Frontiers in Cellular Neuroscience and writing insightful and well-positioned review articles (e.g. Escartin and Rouach, 2013, Astroglial networking contributes to neurometabolic coupling. Frontiers in Neuroenergetics).

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

Many of the methods and approaches developed by team 1 are novel and original, including viral-based gene transfer models, microMRI and molecularly-targeted MRI. The team plans to use these techniques to measure early metabolic dysfunctions in ND (Neurodegenerative disease) in humans. The projects have a strong biomedical focus and the close interactions of team 1 members with the more clinical teams and also the Henri Mondor Hospital, undoubtedly facilitates translation of promising methods (biological and imaging) from bench to clinic. Although team 1’s activity is mainly academic, they have a number of industrial collaborations (e.g. Servier, Eli Lilly). These collaborations will place the Team in a good position to exemplify findings in the lab into potential clinical products.

The participation in a range of public engagement activities by several members of Team 1 is excellent. They have participated in a number of activities directed at increasing public awareness and understanding of the research conducted by URA 2210.

Assessment of the unit's organisation and life

Team 1 plays an essential role in providing basic science projects and the preclinical imaging development for the identification of novel therapeutic strategies in neurodegenerative disease. The cross-cutting themes of the unit facilitate integration of Team 1’s activities into the unit as a whole.

Representatives of Team 1 are involved in regular team meetings, as well as cross-cutting steering committees.

Assessment of the unit's involvement in training through research

The unit has a strong student population, and team 1 in particular has trained a considerable number of students over the past 5 years; 5 completed and 6 currently in progress. The attractiveness of the team is high, as assessed by PhD students applying from abroad (Canada). They also attracted 5 over the fifteen national CEA grants for PhD. Given the successful completion of several students, guidance and quality of supervision is likely high. Both PhD students and post-docs have gone on to continue with scientific careers on leaving MIRCen, whilst previous Masters students in the lab have gone on to PhD studentships either at MIRCen or elsewhere. Several of Team 1 members are involved in co-ordination of the Masters teaching modules.

Assessment of the strategy and the five-year plan

The proposed programme will build on previous work, around the central hypothesis that the convergence of damage developed within multiple cell types, including glial cells, is crucial to the selective neuronal dysfunction occurring in neurodegenerative diseases. The work will focus particularly on metabolic interactions between cells, and will use a variety of tools including viral vectors, cell sorting, animal models, in vivo cell and animal imaging. The team plans to extend their previous findings and methods in HD to both AD and PD over the coming years.

The proposal describes a number of imaging and spectroscopy approaches that will be implemented or developed to address biological questions. Several of these methods reflect new developments and are quite challenging – for example, the developments in diffusion weighted MRS (Magnetic Resonance Spectroscopy) will push the boundaries of what is possible with this method, which by necessity carries some risk. Nevertheless, the potential benefits could be substantial if it is indeed possible to obtain information at the cellular scale in models of neurodegeneration. The 13C MRS methods are well established by Mr Julien VALETTE and the collaboration with Mr Pierre-Gilles HENRY in Minnesota will further strengthen this element of the proposal. The use of both FRET (Fluorescence Resonance Energy Transfer) metabolic nanosensors and 17O imaging have potential for yielding very interesting data, and will complement existing metabolic measurements.

The work describing the consequences of reactive astrogliosis and astrocyte function per se in neurodegenerative disease is both novel and timely, and few other groups are working in similar areas. Increasing interest has focussed in recent years on the role of astrocytes in mediating and modulating neuronal function and associated vascular and metabolic responses. The natural, but currently understudied, extension of these concepts is the impact of the astrocyte inflammatory response during disease on normal functioning of these processes. Understanding how astrocytes contribute to neurodegenerative diseases, both directly and indirectly, may be critical to effective treatment. Moreover, extending this idea into the regional vulnerability projects and the possibility that different astrocyte populations respond differentially is an exciting concept – it is not clear whether the team also plans to look at different reactive astrocyte phenotypes, rather than just reactivity per se in different regions, but this is also an emerging concept and may be important in this context.

During the site visit, the Team members clarified the interactions between methodological and biological aspects of this programme, and on the basis of previous experience and output, all elements of the programme are very likely to be achievable. The only significant concern on the part of the reviewer's was the breadth of proposed projects, and the likelihood that the team might be overstretching themselves. Nevertheless, it was recognised that translating their previous developments and findings in HT into other neurodegenerative diseases was a logical progression of their work.

Conclusion

Overall, the opinion of this team is excellent. It is clear that work within this part of the unit into the pathophysiological mechanisms of cell death and dysfunction will underpin many of the downstream clinical studies, and provide important insight into the biology underlying the imaging biomarkers. The research proposed by the team is likely to attract further funding and industrial partnerships.

- **Strengths and opportunities:**

Multi-level approach from cells, through animal models to man (in collaboration with other teams).

Multiple techniques allowing understanding of molecular, cellular and whole organism level biology.

Development of new imaging methods that have potential for clinical translation and validation in preclinical models.

- **Weaknesses and threats:**

Slight lack of focus in overall direction broad range of projects.

- **Recommendations:**

Prioritise projects to develop clearer overall focus and avoid over-stretching the team.

Team 2 : Preclinical and clinical therapeutics for neurodegenerative diseases

Name of team leader: Mr Philippe HANTRAYE

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	5	5
N3: Other permanent staff (without research duties)	12	13
N4: Other professors (PREM, ECC, etc.)	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1
N6: Other contractual staff (without research duties)	2	2
TOTAL N1 to N6	**22**	**23**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students		
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	2	3

• Detailed assessments

Assessment of scientific quality and outputs

The main activities of team 2 are focused on developing, assessing and validating innovative strategies for neurodegenerative diseases (ND) including Huntington's (HD), Parkinson's (PD) and Alzheimer's (AD). One particularity and originality of this team is modelling ND in large animals using gene transfer techniques. Hence, these models can be used to develop new PET imaging tracers for early stage neurodegenerative events and develop new cell-based and gene-based therapeutic strategies, in particular for the treatment of PD and HD.

In the past 4 years the team developed mainly two animal models:

1) a genetic primate model of HD based on gene transfer (first with a lentivirus and more recently with AAV5 serotype) of a mutated form of the Huntingtin gene (171 a.a. N-terminal fragment of Htt with 82 glutamines stretch) in the caudate-putamen;

2) two models of tauopathy based on the somatic gene transfer of a mutated form (P301L) form of the human tau gene in the hippocampus of adult rat of non-human primates.

These models constitute an important translational output since they allow the development of more pertinent and more predictive animal models of these ND, and can provide the opportunity to characterize early biomarkers along with the possibilities to test new therapeutic strategies.

In this way, the CEA environment provides a unique opportunity for developing and validating, besides classical pharmacological tracers, new PET tracers, based on non-conventional targets (amyloid plaques, neurofibrillary tangles, huntingtin aggregates, Lewi Bodies) that are in a R&D pipeline under patent. The team has an excellent involvement in MIRCen's platforms (pre-clinical Imaging Platform for Gene and cell therapy).

The team has a good publication record with 77 published papers during the past five years, an average citation per item of 12 (PNAS, J. cerebral blood flow Metab, Neurobiol Aging, Neuroimage, Lancet, Plos One, Human mol Genet, J Neurosc, etc).

The Impact factor of main publication journals is of good level. In addition, the team had a very recent publication in the Lancet journal in which four team members are co-authors. This study concerns a clinical trial in PD patients using ProSavin, a new gene transfer approach aimed at restoring DA synthesis and release in the striatum. The authors participated significantly to the pre-clinical studies in non-human primates, and brain imaging in human. Although several papers are signed in first author position by team members the committee noted that only few publications are signed as last authors by the team members (including the team leader) and the large majority are in collaboration. It appeared that a major part of the activity of the team was devoted to platform activities in the field of ND research.

Assessment of the unit's academic reputation and appeal

The team leader has numerous national and international academic collaborations, and also industrial collaborations (3). The team members are very active in European networks (8 EU grant applications). The team leader is the coordinator of NeurATRIS that gathers five nodes (MIRCen, ICM/IHU Salpétrière, Henri Mondor Hospital, Kermlin Bicêtre and B.I.R.D.) and is the French part of the large European translational consortium EATRIS. Thus, the team appears to have a large international and national visibility being at the centre of several major projects and scientific programs.

This is in contrast with the apparent fact that, during the 5 past years, the team leader participated to only two international conferences (one of them as a chair), which is surprising when considering his unique expertise and reputation in the field of gene therapy for ND in non-human primates and brain imaging.

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

The team's interaction with the social economic and cultural environment is outstanding, with translational activities built upon strong collaboration with clinical investigation, pharmaceutical companies and international networks. A collaboration in continuity with the initial experiments performed in non-human primates, a phase 1/II trial of ProSavin®, a dopamine replacement gene therapy strategy for the treatment of PD in Europe has been published very recently in The Lancet journal and has received a wide media coverage. Translational activities also concern new cell and gene therapy approaches in HD (cell grafts and lentiviral CNTF transfert).

Three patents have been recently licenced by the team, with eight industrial collaborations (Ipsen; Servier; Oxford Biomedica ; Hoffman-LaRoche; Braingene), and long lasting collaborations with Big pharmas (Sanofi, Servier).

The team leader has exceptional public engagement activities by participating in scientific committees (ANR, Scientific board of Dim biotherapy and Dim neurosciences, ITMO Neurosciences, ENP, JPND, PI of NeurATRIS; Arc, etc). He is also member of the strategic management of MEDICEN PARIS REGION (responsible for the imaging area). The team leader and several team members are strongly involved, as heads for example, in MIRcen's platforms.

The team members participate actively to lay ("grand public") manifestations, including writing articles for lay audience or participating to press conferences.

Assessment of the unit's organisation and life

Excellent involvement in MIRCen's platforms.

Team 2 members are involved in regular team meetings as well as cross-cutting steering committees

Assessment of the unit's involvement in training through research

The team is not very much actively involved in training through research as only few PhD thesis were recently defended and few PhD students are currently present within this team. A post-doc fellow from the team was recruited as the head of the rodent behavioural platform in MIRCen. Another post-doc was recruited in 2013 as a Research Scientist at Servier. (Only 1 PhD student completed his PhD).

Assessment of the strategy and the five-year plan

For the coming period, the main activities of team 2 will focus on animal modelling, PET imaging and experimental therapeutics, following a continuum of translational research ultimately aiming at clinical phase I/II trials.

Three main topics will be pursued:

1) translational research in HD, owing to the transfer of AAV5 gene overexpressing the N-terminal part of the mutant Htt in the caudate putamen of non-human primates. Characterization of this new animal model will be performed at different time points with a study of relationships between striatal territories injected and the behavioural impairments. The PET imaging will be used to study the progression rate of striatal neuronal loss, pre-synaptic loss of function and the neuroinflammation/astrocytic reaction;

2) translational research in AD: development of the rat and primate models of Tauopathy. The preliminary results have allowed to assess the biodistribution and neuronal specificity of AAV9) CBA construct overexpressing the wild type or tau gene in the hippocampus and projection areas, like the cingulate cortex. Imaging and behavioural analysis will be performed in a large cohort of primates. Proteomic analysis will be performed in collaboration with Lille in order to measure peripheral biomarkers of the progression of tauopathy, with the final goal to follow up patients for the evaluation of new therapies and specificity of existing and novel PET tracers to be used in the clinic to follow disease progression;

3) New PET tracers for ND: owing to financial support obtained through NeurATRIS initiative, implementation of a cyclotron and laboratories for the production and radiochemical labelling of compounds with carbon 11 and Fluorine 18. These tools will allow PET imaging of the parkinsonian state, proteopathies (synucleopathies, tauopathies and AD).

These ambitious projects clearly represent translational activities in which the team has a recognized expertise. However, a lack of in depth study of mechanistics is to be noted. Nevertheless, the projects present significant interest, for optimizing gene therapy, imaging, identifying biomarkers in ND.

In HD, some innovative projects were presented with the grafting of iPS cells in the HD primate model for example. However, there was little information about the advancement of the projects (are the iPS cells really differentiated into striatal neurons apart from DARPP32 expression?).

The transplicing therapeutic strategy is proposed in order to selectively silence the mutated Htt. In this project, gene reprogramming at mRNA level is proposed using a strategy based on spliceosome-mediated RNA transplicing (SmaRT). Although challenging, and requiring innovative cellular models, this project is highly innovative and promising. It clearly demands for driving forces, for example PhD or post-doc, in addition to the researcher in charge.

Preclinical innovative therapeutic strategies in PD with an adjustment of the gene transfer approach to individual's needs, and the use of "regulatable" constructs are not convincing as previous published studies in rodent and especially in non-human primates proved that the method was not efficient and without benefit.

Conclusion

- **Strengths and opportunities:**

- development of non-human primate models;

- original gene therapy approaches;

- new tools for PET imaging;

- strong environment;

- unique expertise for brain imaging in primates;

- strong potential for translational activities;

- significant national and european visibility.

- **Weaknesses and threats:**

Too many projects, some of them (the more fundamental ones) merit a more in-depth attention, and/or forces (students, Post-docs).

- **Recommendations:**

Prioritisation of projects to avoid becoming solely a technical platform.

Several young researchers/engineers were recently recruited with a CEA position within this team. They have the potential to become in time quite independent and perhaps leading some of the projects that were presented. These researchers should be encouraged to supervise PhD students, seek for independent fundings specifically aimed at young researchers early in their career, and become, when ready, project leaders within this team.

Team 3 : Multimodal Imaging of Neurodegenerative Diseases models

Name of team leader: Mr Marc DHENAIN

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	2	2
N3: Other permanent staff (without research duties)	3	3
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2
N6: Other contractual staff (without research duties)	1	1
TOTAL N1 to N6	**8**	**8**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	2

• Detailed assessments

Assessment of scientific quality and outputs

The "Multimodal Imaging of Neurodegenerative Diseases" team led by Mr Marc DHENAIN has recently been founded as part of the re-organization of the URA 2210 unit. In the previous 5 years, Mr Marc DHENAIN and his current team members were part of the "Preclinical Brain Imaging" team led by Mr Vincent LEBON. Overall, the "Multimodal Imaging of Neurodegenerative Diseases" team is smaller than the original "Preclinical Brain Imaging" team, as several team members and their research projects have now been incorporated into a different team (Cell-Cell interaction in neurodegeneration).

Over the last 5 years, the members of the newly-constituted Multimodal Imaging of Neurodegenerative Diseases team have successfully implemented MR microscopic imaging methods to detect and monitor progression of amyloid plaques in several animal models of AD. They have also put a significant effort into the development of post

mortem imaging in primates and rodents and brain imaging protocols to co-register MRI and PET images with 3D post mortem data. Finally, using in vivo and post mortem imaging techniques, the group has contributed to identify several biomarkers of aging in the mouse lemur primate and to assess the effect of anti-amyloid therapies and other therapies in preclinical models of AD.

This research effort resulted in an excellent number of methodological and preclinical publications in peer-reviewed journals with a very good impact factor including PNAS, Plos One, Neuroimage, Neurobiology of Aging, Journal of Neuroscience, etc (41 papers, Average Citations per Item: 5.61, h-index: 10).

Compared to the other teams, the group has not published any very high impact paper. However, the committee acknowledges that the nature of their work, although crucial for preclinical research, is too specialist and technical to target journals with very high impact factor.

Assessment of the unit's academic reputation and appeal

The development of post mortem imaging and imaging protocols to co-register in vivo and post mortem imaging findings has given to the team an incontestably international recognition. Results of their studies have been presented at several international Conferences/Congresses. Mr Marc DHENAIN has been invited to give lectures at several national and international conferences.

There are very strong industrial collaborations with several pharma companies and the team has already attracted a considerable level of both pharma and public funding in several areas of their proposed programme of work.

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

Similarly to the other two teams, the main research focus of the "Multimodal Imaging of Neurodegenerative Diseases" team is on Neurodegenerative diseases. These chronic and progressive conditions represent one of the leading medical and societal challenges faced by our society.

The team has many internal and external collaborations including the Institut Pasteur, the ICM (Institut du Cerveau et de la Moelle épinière) and the Hoffmann-LaRoche laboratories. As mentioned before there is a strong connection with industry.

Mr Marc DHENAIN has given many general presentations on ongoing research and therapies of Alzheimer's disease.

Assessment of the unit's organisation and life

The team seems to be perfectly integrated into the URA 2210 unit. There is a clear synergistic collaboration between the three teams. There are regular team, project and platform meetings which will ensure integration across teams and increase strength of approach. Team 3 is an essential component of the unit as a whole in establishing links between the preclinical and clinical efforts, particularly with respect to image analysis and development of imaging biomarkers.

Assessment of the unit's involvement in training through research

The original "Preclinical Brain Imaging" team had a significant role in academic research and student training. The newly-constituted Multimodal Imaging of Neurodegenerative Disease trained 6 PhD students (5 defended), 12 masters, and 4 engineers/post-doctoral fellows. This represents ~40 % of the total number of supervised students in the lab. We notice that Mr Marc DHENAIN is involved in the coordination of Paris area Doctorate Schools (ED n°419, ED n°158, ED n°425) and University Diploma (since 2013), Kremlin–Bicêtre, "Translational Research in Neurological disorders". He also serves in thesis and HDR committees.

Assessment of the strategy and the five-year plan

Over the next five years the team intend to continue and extend their previous work on methodological developments in brain imaging at the preclinical level. Studies in AD patients will also be started.

The main focus will be on the cross correlation between different imaging modalities and the development of appropriate imaging biomarkers of neurodegeneration. This structure will provide greater interaction between the preclinical and clinical elements of the unit and pull together the imaging strategy across the whole.

The proposed work on amyloid plaque imaging is well-funded, and although there are few specific details of the methods to be used, or hypotheses to be tested the level of current funding indicates that this aspect of the proposal is competitive and novel.

Another important aspect of their work will be the co-registration and correlation of in vivo imaging findings with post mortem histology. This is a very novel and intriguing field. It should be noticed that other groups are also working in this area. Nevertheless, application to the neurodegenerative diseases in question is novel and important.

The section on animal models and therapies seems a little fragmented and the overall goals or direction less clear. Nevertheless, there are some interesting and novel concepts. In particular, the role of mast cells in AD pathology is a new and interesting avenue, as is identifying the mechanisms by which immunotherapy reduces amyloid load – both questions could lead to more or improved therapies in this area.

Conclusion

Overall, the opinion on this team is very positive. Development of multimodal Imaging protocols and identification of sensitive imaging biomarkers of the neurodegenerative process are crucial steps for both preclinical and clinical research in this field. The research proposed by the team could lead to significant advancements in brain imaging techniques, which will also benefit the other two teams and attract pharma/industrial patterns.

- **Strengths and opportunities:**

- strong and long-standing collaboration with scientists of the other teams;

- unique expertise in 3D analysis of tissue sections;

- strong training record;

- strong clinical element. This will allow translation of other programmes into clinic;

- great potential for developing and validating imaging techniques with clinical and industrial applications.

- **Weaknesses and threats:**

The team is relatively small, particularly considering that the proposed programme is complex and covers different aspects including methodological developments, preclinical and clinical research. The team also intend to extend their focus to the degenerative process in Huntington's disease and Parkinson's disease. There is a plan to recruit a young researcher on a permanent position.

Coherence of overall goals is unclear.

- **Recommendations:**

The proposed programme would very much benefit from the recruitment of 1 or 2 additional researchers.

5 • Conduct of the visit

Visit date:

Start: Wednesday, 08 January, 2014 at 9.15 a.m

End: Wednesday, 08 January, 2014 at 6.00 p.m

Visit site: LMN

Institution: CEA-CNRS
URA CEA-CNRS 2210
Molecular Imaging Research Centre (MIRCen)
Institut d'Imagerie BioMédicale
Direction des Sciences du Vivant
CEA-18 route du panorama
B.P.6 92265 Fontenay-aux-Roses, France

Conduct or programme of visit:

09h15	Welcome breakfast
09h30	Door closed meeting - Presentation of the AERES to the experts committee by the Scientific Delegate of AERES (DS) (Conference room R+2)
09h45	Presentation of the experts committee and of AERES to the unit by the DS
10h00–10h45	Director of the unit Presentation of the past activities and project (Mr Emmanuel BROUILLET)
10h45	Scientific assessment and projects, team 1 Mr Gilles BONVENTO - "Cell-cell interactions in neurodegeneration"
11h15	Coffee break
11h30	Scientific assessment and projects, team 2 Mr Philippe HANTRAYE - "Preclinical and clinical therapeutics for neurodegenerative diseases"
12h00	Scientific assessment and projects, team 3 Mr Marc DHENAIN - "Multimodal Imaging of Neurodegenerative Diseases models"
12h30	Lunch with all laboratory staff ("buffet" on site)
13h30	Meeting with the representatives of the institutions *Audience: members of the expert committee and DS*
14h00-15h00	Meeting with permanent and non permanent staff: - Meeting with the technical staff *Audience: members of the expert committee, DS and ITA representatives of the organisms (conference room, R+2 MIRCen)* - Meeting with PhD students and post-docs and/or fixed-term contract researcher, engineers. (Meeting room R+2 MIRCen) *Audience: members of the expert committee and DS* - Meeting with researchers, teacher and researchers (meeting room, R+1 MIRCen) *Audience: members of the expert committee and DS*
15h00	Meeting with the representative of the « École Doctorale ED n°419 » *Audience: members of the expert committee and DS*
15h15	Break
15h30	Discussion with the head of the unit *Audience: members of the expert committee and DS*
16h00-18h00	Door closed meeting

6 • Supervising bodies general comments

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Le président de L'Université Paris-Sud

A

Monsieur Pierre GLAUDES
Directeur de la Section des Unités de recherche
AERES
20 Rue Vivienne
75002 PARIS

Présidence
Bât 300
91405 ORSAY Cédex

president@u-psud.fr

Orsay, le 04 Mars 2014

Réf : 35/14/JB/LM/AL

Objet : Rapport d'évaluation d'unité de recherche
N° S2PUR150007648

Monsieur le Directeur,

Vous m'avez transmis le 12 février dernier, le rapport d'évaluation de l'Unité de recherche – Laboratoire de maladies neurodégénératives : mécanismes, thérapies, imagerie – URA2210 – N° S2PUR150007648 et je vous en remercie.

L'Université, qui pourrait devenir tutelle de l'unité dans un avenir proche, prend bonne note de l'appréciation et des suggestions faites par la Comité.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de ma sincère considération.

Le président de l'Université Paris-Sud

UNIVERSITÉ PARIS SUD
PRÉSIDENCE
Bâtiment 300
91405 ORSAY cedex

Professeur Jacques Bittoun

Neurodegenerative Diseases Lab
URA CEA-CNRS 2210
Life Science Division
Molecular Imaging Research Center

Fontenay-aux-roses, le 3 mars 2014

Objet : Rapport AERES E2015-EV-0912281K-S2PUR150007648-006570-RT, Neurodegenerative Disease Laboratory - **Answer from the Director**

Dear Colleagues,

The director of the research Unit, on behalf of all the researchers of the Unit, is grateful to the AERES committee and his chairman for his in depth and detailed analysis of our research activities and projects and his very positive comments.

The committee acknowledged the excellence of the Unit's productivity in terms of publications, patents, and services at the preclinical and clinical levels. The committee also noted our strong interaction with the environment through national and international collaborations and partnerships, especially with pharmaceutical industries. The key role played by the researchers of the Neurodegenerative Diseases Laboratory in teaching and supervising young scientists has been also underlined. The committee also emphasized that the state-of- the-art equipment whose the Unit is in charge in the different platforms of MIRCen is a key strength in our project.

The committee pointed out that the wide diversity of research projects of our three teams may be overstretching considering the workforce in presence. This reflects the ambition of our research program and the high enthusiasm and motivation of our researchers. The director of the Unit and the team leaders will make their utmost efforts, with the help of our institutions, to secure the feasibility of the envisioned projects through different actions, including the recruitment of young researchers.

Emmanuel Brouillet, PhD
Head, Neurodegenerative Diseases Laboratory,
Molecular Imaging Research Center (MIRCen)
Institute for BioMedical Imaging (I^2BM)
Life Science Division, CEA

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Monsieur Pierre GLAUDES
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

Fontenay-aux-Roses, le 4 mars 2014
Objet : Rapport AERES E2015-EV-0912281K-S2PUR150007648-006570-RT,
Neurodegenerative Disease Laboratory
N/Réf. : DSV/DIR/2014-097/ADLC/guc

Dear Sir,

I thank the AERES committee for his comprehensive evaluation of the scientific activities of the Neurodegenerative Disease Laboratory (URA2210) that is under supervision of CEA and CNRS. The committee underlines the scientific high quality of this unit and its unique gathering of scientists experts using multidisciplinarity methodologies. Recommendations will be taken into account and discussed in a constructive way with the scientific unit leader.

The committee has highlighted the pivotal role of this laboratory in the academic and industrial environment interested in translational research in Neurosciences. I would like to further emphasize that URA2210, hosted at MIRCen, is a central actor in the management of the different platforms of this CEA/INSERM service. MIRCen has emerged from scientific background and know-how of URA 2210. Thus, when opening MIRCen, we believed that involving part-time academic researchers and engineers of URA2210 for running these platforms was the most efficient way to maintain at its highest level the scientific excellence of these platforms, to the benefit of the Neuroscience community implicated in the translational research. The evaluation achieved by the AERES experts shows that this strategy has been successful, considering that both the academic research productivity of the URA2210 and its interaction with its partners in translational Neurosciences has been judged excellent.

Yours faithfully,

Gilles BLOCH

Commissariat à l'énergie atomique et aux énergies alternatives
Centre de Fontenay-aux-Roses | 18 route du Panorama | BP 6
92265 Fontenay-aux-Roses Cedex
T. +33 (0)1 46 54 94 67 | F. +33 (0)1 46 54 78 48
gilles.bloch@cea.fr
Etablissement public à caractère industriel et commercial | RCS Paris B 775 685 019

Direction des sciences du vivant
Le Directeur