Toxicologie pharmacologie et signalisation cellulaire

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Toxicology, Pharmacology and Cell Signaling

Under the supervision of the following institutions and research bodies:

Institut National de la Santé Et de la Recherche Médicale

Université Paris Descartes

January 2013

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

Research Units Department

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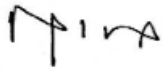


Pierre Glaudes

The president of AERES "signs[...], the evaluation reports, [...]countersigned for each evaluation department by the relevant head of department (Article 9, paragraph 3, of french decree n°2006-1334 dated 3 november 2006, revised).

Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).
This score (A+, A, B, C) concerned each of the six criteria defined by the AERES.
NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

Criterion 1 - C1 : Scientific outputs and quality ;
Criterion 2 - C2 : Academic reputation and appeal ;
Criterion 3 - C3 : Interactions with the social, economic and cultural environment ;
Criterion 4 - C4 : Organisation and life of the institution (or of the team) ;
Criterion 5 - C5 : Involvement in training through research ;
Criterion 6 - C6 : Strategy and five-year plan.

With respect to this score, the research unit concerned by this report and its in-house teams received the following grades:

- Grading table of the unit: Toxicology, Pharmacology and Cell Signalling

C1	C2	C3	C4	C5	C6
A+	A	A	A+	A+	A

- Grading table of the team: Toxicology Signaling and Metabolism

C1	C2	C3	C4	C5	C6
A	A	A	A+	A+	A

- Grading table of the team: Pharmacology, Toxicology, and Cell Signalling of Cartilage and Intervertebral Disc

C1	C2	C3	C4	C5	C6
A	A	A	A	A+	A

- Grading table of the team: Mitochondrial disorders : pharmacological therapy and metabolic signaling

C1	C2	C3	C4	C5	C6
A+	A	A+	A	A	A

- Grading table of the team: Pharmacotoxicology and Structural Biology

C1	C2	C3	C4	C5	C6
A+	B	A	A	A	A

- Grading table of the team: Stem cells, signaling and prions

C1	C2	C3	C4	C5	C6
A+	A	A	A	A	A+

- Grading table of the team: Signaling and neurological pathophysiology

C1	C2	C3	C4	C5	C6
A+	A	NN	NN	NN	A

- Grading table of the team: Mechanism of interferon action and biotherapeutic pathways

C1	C2	C3	C4	C5	C6
A	A	A+	A	A	A

- Grading table of the team: New Therapeutic Approaches of Myelination

C1	C2	C3	C4	C5	C6
A+	A	A	A+	A+	A+

- Grading table of the team: Neuromuscular degeneration and plasticity

C1	C2	C3	C4	C5	C6
A	A	A	A+	A+	A+

Evaluation report

Unit name:	Toxicology, Pharmacology and Cell Signalling
Unit acronym:	
Label requested:	UMR-S
Present no.:	UMR-S 747
Name of Director (2012-2013):	Mr Robert BAROUKI
Name of Project Leader (2014-2018):	Mr Robert BAROUKI

Expert committee members

Chair:

Mr Serge NEF, University of Geneva, Switzerland

Experts:

Ms Monique ALRIC-LOMBARDY, University of Clermont-Ferrand 1 (representative of CNU)

Mr Robin FRANKLIN, University of Cambridge, UK

Mr André GUILLOUZO, University of Rennes

Mr Bernard JASMIN, Ottawa University, Canada

Mr Zaal KOKAIA, Lund University, Sweden

Ms Marie-Hélène LAFAGE, University Saint Etienne

Mr Pierre MARQUET, University Limoges (representative of INSERM)

Ms Claire RODRIGUEZ-LAFRASSE, University Lyon 1

Mr Bernard SALLES, University of Toulouse

Mr Pier Paolo SCAGLIONI, University of Texas Southwestern Medical Center, USA

Mr Charles THOMAS, University of Bourgogne

Scientific delegate representing the AERES:

Ms Paule VASSEUR

Representative(s) of the unit's supervising institutions and bodies:

Mr Frédéric DARDEL, University Paris Descartes

Mr Nicolas JEANJEAN, INSERM

1 • Introduction

The evaluation and site visit took place on January 16th to 17th, 2013 in Paris, at the UFR Biomédicale des Saints-Pères, University of Paris Descartes. The visit was well prepared, with two detailed documents describing the 2007-2012 past-activities and the 2014-2018 scientific projects provided in advance. At the start of the visit, a booklet was also provided which included all the slides of the presentations as well as an update on the recent publications and grants obtained since October 2012.

The committee had sufficient time, albeit in a very tight schedule, to discuss various issues. The visit was executed smoothly and without any problems. Although no visit of the labs had been planned, some members of the committee took the occasion to visit some laboratories and discuss with their members.

History and geographical location of the unit

Unit 747 was created on Jan 2006. It consisted initially of three teams (teams 1-3) which was then expended with two additional teams (4 and 5). Successful internal recruitment within team 5 has led to a spin off with two distinct projects and teams (5 & 6). Finally, due to close interations and relevant expertise, teams 7, 8 and 9 have been proposed to join the unit 747.

The 9 teams participating to this project are localized in the same building of the Université Paris Descartes at 45 rue des Saints-Pères. The surface on which the research unit work is important, about 1500 m2 and distributed on 3 floors.

Management team

The unit is/will be managed by:

1) The research unit Director with the help of an administrative assistant and a secretary

2) A unit council which will make major decisions concerning allocation of funds, etc. This council includes elected and appointed members and represents all teams and categories of personnel

3) A general assembly including all personnels to discuss the evolution of the unit

4) Monthly informal meetings with team leaders concerning scientific and administrative issues

5) An external scientific advisory board (SAB) to assess the unit progress and provide input on scientific orientation

AERES nomenclature

Principal : SVE1_LS3

Secundary : SVE1_LS4, SVE1_LS7, SVE1_LS1

Unit workforce

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	27 (11.3)	30 (12.9)	25 (11.2)
N2: Permanent researchers from Institutions and similar positions	17	15	15
N3: Other permanent staff (without research duties)	17 (14,7)	17 (14,9)	
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	2	1	1
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	8	8	5
N6: Other contractual staff (without research duties)	2 (1.2)	3 (2.2)	
TOTAL N1 to N6	73 (54,2)	74 (54)	

Percentage of producers	***100 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	28	
Theses defended	34	
Postdoctoral students having spent at least 12 months in the unit*	10	
Number of Research Supervisor Qualifications (HDR) taken	5	
Qualified research supervisors (with an HDR) or similar positions	33	31

2 • Assessment of the unit

The unit consists of nine autonomous teams that could be best described as a department of Molecular and Cellular pharmacology and Toxicology. These Teams are united by a set of common objectives to identify pharmacological and toxicological targets based on expertise in signaling in different tissues or cells. More precisely, the unit's projects address important basic issues such as cellular detection of and response to toxic and infectious agents as well as the molecular and cellular mechanisms leading to diseases such as neurological, metabolic, infectious and joint diseases.

Overall, the research carried out at the unit 747 can be qualified as excellent. The success of the unit is based on the complementary expertise of the different teams that encompass basic and translational research, various cell signaling pathways or molecules (AhR, Sirtuins, prions, Gsk3, miRNAs, interferons, Wnt) as well as biological processes and diseases (metabolism, arthritis, neuroscience, myelinisation). This diversity in research topics and expertise could potentially be a weakness if the level of interaction and integration is low. However, it is quite clear that the teams composing Unit 747 seized the opportunity of a multi-team structure to stimulate daily contacts, catalyze numerous collaborative projects and promote the submission of ambitious projects for funding based on complementary expertise, shared concepts & methodologies and common objectives.

The general assessment of the research unit is extremely positive:

1) The unit has been very successful over the past four years at building common objectives, shared concepts and developing interdisciplinary projects.

2) High publication output: the intrinsic qualities of each team, together with the scientific interactions led to numerous and sometime prestigious publications in high impact journals.

3) The unit 747 has also shown significant success in attracting external funding; mostly national funds, more rarely international funds.

4) International recognition and visibility of most PIs is also obvious based on the number of invited lectures.

5) All teams and PIs are strongly implicated in different aspects of teaching and take good care of their PhD students.

6) The atmosphere and the general spirit were felt to be extremely positive, with unanimous and enthusiastic backing of the structure and future of the unit.

7) Strong support from the two managing bodies (University Paris Descartes and INSERM).

Based on the five years research plan and their strong expertise in cell signalling, toxicology/pharmacology, the unit is in an optimal position to identify relevant drug and toxicant targets. Overall, the strategies and plans designed by individual teams could be described as solid, coherent and scientifically sound. These projects tackle mostly original and relevant questions and take advantage of existing complementary expertise and original data. This should lead to a better assessment of chemical toxicity and the identification of novel therapeutic tools for highly relevant diseases such as neurological, metabolic, infectious and joint diseases.

Strengths and opportunities

1) Very good publication record both in terms of quality and quantity (261 publications reported). Some papers being published in top journals such as *Science* (Teams 5&6), *Nature* (Team 4), *N Engl J Med* (Team3), *PNAS* (Team 8), *J.Neurosc.* (Team 9), *Environmental Health Perspectives* (Team 1), *Arthritis and Rheum* (team 2), *J. Virology* and *Mol. Cell. Proteomics.* (Team 7). Although the publication production is variable between teams due to their size and age, all teams are aiming for quality publication with success.

2) Association of competences in basic research and translation research, complementary expertise in signaling pathways, biochemistry, molecular biology, toxicology and pharmacology.

3) The good state of mind of the personnel at all levels such as engineers, Ph.D. students, post-docs, technical and administrative staff.

4) Interdisciplinarity and enthusiasm for scientific projects are two major characteristics arising from the visit. This is reflected by a very good scientific communication between scientists at all level (PhD students, post-docs, technicians and engineers, permanent scientists).

5) Numerous diversified sources of funding (such as the ANR) in addition to institutional funding.

6) Involvement in numerous scientific committees, regional and national scientific networks (Antiopes toxicology network, Eriche network, chem&tox), national institutes (IFR Institut medicaments toxicité chimie environnement), national and international collaborations.

Weaknesses and threats

1) Lack of international fundings, in particular EU funds.

2) Involvement in relatively few international scientific networks.

3) Reduced financial support by institutional or private national sources might affect negatively funding in the coming years and reduce the competitiveness of the unit as a whole.

4) Administrative ressources are insufficient. Too much time is spend by PIs (principal investigators) and researchers on administrative tasks distracting them from more productive activities related to research.

5) Teaching represents a heavy burden.

6) Due to past and future retirements, a shortage of administrative, technical and scientific staff is forecasted unless hiring rates are maintained.

7) Dispersion of topics may alter the coherence of the project. The diversity in subjects and fields of research among the different teams represents a strength but could be also seen as a weakness if the teams are not collaborating and start to disperse with methods and concepts that are not relevant for the unit.

Recommendations

The Committee recommends:

1) To pursue and encourage interactions and a strong collaborative mindset between laboratories of the unit.

2) To develop and strengthen international scientific networks and links with laboratories working in related topics (i.e., toxicology/pharmacology/cell signaling).

3) To maintain and, if possible, extend the levels of financial resources in particular by securing European and international sources of fundings.

4) Strategic vision: to recruit an additional team focusing on chemical toxicology.

5) Strategic vision: to increase the level of innovation by embracing novel technologies. For example by developing services enabeling genome wide approaches and bioinformatic support within the unit due to the emergence of high throughput sequencing for expression studies.

6) Strategic vision: to set up and implement an external, international Scientific Advisory Board to provide independent inputs on scientific projects and future orientations.

7) Strategic vision: set up a mentoring system for young promising PIs.

3 • Detailed assessments

Assessment of scientific quality and outputs

The relevance and the originality of the research are excellent. The unit has a very strong publication record for the period 2007- mid 2012. This includes 261 publications with some papers being published as first authors or corresponding authors in high impact factor journals such as *Science* (Teams 5&6), *Nature* (Team 4), *NEJM* (Team 3), *PNAS* (Team 8) or top specialized journals including *J.Neurosc.* (teams 8, 9), *EHP* (team 1), *Arthritis and Rheumatism* (team 2), *J. Virology* and *MCP* (team 7) to name a few.Some publications, although not published in these top journals, represent landmark papers in their respective fields (e.g. team 9). Among individual teams, the production is usually of high quality although variable in terms of quantity, but this aspect is directly correlated with the size, age and the publication strategy pursued by each team.

The outstanding scientific quality and visibility of the unit is also reflected by the numerous invitations to congresses and international conferences (i.e. ≥100).

Assessment of the unit's academic reputation and appeal

The visibility and reputation of the unit and individual teams is excellent both at the national and international levels. This includes:

1) As mentioned above, more than 100 invitations to congresses and international conferences.

2) Significant involvement in the organization of international meetings either as chairman or board-member: chair PPTOX III 2012 Paris (head of unit 747); chair SAC meeting of the ISTC, Moscow 2008 (head of unit 747); co-chair of the world congress on osteoarthritis, OARSI San Diego 2011 (head of Team 2); chair of the world congress on osteoarthritis, OARSI Barcelona 2012 (head of Team 2); chair of the international congress "From interferon discovery to mechanisms of action and clinical applications 1957-2007" (head of Team 7).

3) Board members in numerous scientific councils and scientific societies including: board for the INSERM scientific council (head of unit 747); INSERM scientific specialized commission (CSS, head of unit 747); the ANSES scientific council (head of unit 747); the Ineris scientific council (head of unit 747); the NT INRA scientific specialized commission (head of unit 747); board director for an ANR committee (head of unit 747); board of scientific societies such as SPTC, SFBBM, expert for the ANR (leaders of Team 2 and 7), expert for the AERES and the ANRS (head of Team 7), expert for the HAS (head Team 2), member section 23 national committee CNRS (head of Team 7), expert for the FRS-FNRS (Belgium) (head of Team 8).

4) Some members of the unit act as associate editors for journals such as *PLoS ONE* (heads of Team 2 & 6), *Osteoarthritis and Cartilage* (head of Team 2), managing editor for *Frontiers in Bioscience* (head of Team 6)

5) Most members of the unit act as peer reviewers for numerous top quality journals

6) The unit demonstrated in the past few years its capacity to recruit outstanding scientists that later were offered permanent positions. PhD students and post-docs originate from several foreign countries. Another positive aspect is that all post-docs and PhD students have found employment after they left the unit.

7) The Unit 747 is also part of the following networks:

-Local: the unit is a member of the local C2T2S Federation Project, which is composed of the 4 laboratories of the biomedical faculty involved in Chemistry, Pharmacology and Toxicology

-University/PRES: the unit is part of the MediResisTox network, which plan to apply for the PRES call on interdisciplinary programs.

-The teams are also part of several thematic networks at the national (e.g. ANTIOPES,...) and international levels

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

The unit is deeply involved in teaching and education at all levels and in the dissemination of scientific information to the public through the media.

Public and media communication:

The committee wishes to emphasize that the different projects developed within the unit address highly relevant public issues (chemical toxicity, drug resistance/efficiency, identification of drug targets for high incidence pathologies such as metabolic disorders, neurodegeneration/neurotoxicity, inflammation, etc). As such, members of unit 747 took advantage of their expertise and results to share scientific information with the public and media. It includes:

1) Numerous communications in media such as TV and radio broacastings, as well as articles in newspapers.

2) Numerous seminars for the general public upon invitation from INSERM, Universities and organisation.

3) Active participation in "Journée de la Science" at various locations.

4) Elaboration of an "Educational box" in collaboration with the INSERM communication team on drug allergies.

Teaching activities:

Teaching activities and management of science and medical courses represent a major investment in ressources for unit 747. It includes: responsabilities and teaching for several Master Programs, classes of biochemistry and toxicology, organization of 8 teaching units (UE) at the University Paris Descartes, co-responsability of two global year-levels of university teaching (head Team 1), responsability of the Biochemistry UE for the medical student (head of unit 747), coordination of the UE2.2 M1B Biology module at the Centre Universitaire des Saints Pères(head of Team 4), implementation of a new "National Master of Toxicology" for the PRES project, coordinators in the creation of an international Biomedical Engineering master betwen Paris Descartes and Paris Tech (head of Team 2). In addition, the leader of Team 8 is Dean and the leader of Team 9 vice-Dean of the faculty of Biomedical Sciences.

Technology transfer and translational research:

In addition, due to the good mix between basic and translational research, the unit has been able to valorize the work of its 9 teams through technology transfer: 7 patents and one license have been filed during the period.

From bench to bed side: Team 3 has been able to develop pharmacological therapy for patients suffering from inborn mitochondrial disorders.

Assessment of the unit's organisation and life

The atmosphere and the general spirit were extremely positive, with enthusiastic backing of the structure and of the future of the unit.

Interestingly, the unit encourages innovative inter-disciplinary projects by devoting part of its budget to high risk projects or projects at the "proof of concept" stage that cannot be funded at this early stage by external agencies.

Scientific exchanges between members of the unit are promoted by weekly meetings both at the unit level and the team level, as well as through a data/journal club. This system of regular seminars involving both internal and invited speakers is well established, well organized and well attended.

The unit 747 is managed through different structures and committees that allow communication in both directions (i.e. top-down and bottom-up). More precisely, it includes (i) a unit council, (ii) a general assembly including all personnel to discuss the evolution of the unit and (iii) monthly informal meetings with team leaders concerning scientific and administrative issues. Finally, (iv) an external scientific advisory board (SAB) at the level of the federation to assess progress and provide input on scientific orientation. A document "règlement intérieur" defining the internal rules is also available.

The unit is in the process of developing quality management standards as recommended by INSERM. A quality manager has been nominated and a small group composed of laboratory members from different teams is dedicated to improve laboratory practices, data reliability and traceability.

The unit takes advantage of numerous platforms either developed internally (protein production and crystallography, mechanical stress/Flexercell) or externally (genomic platform, small animal imaging, proteomics platform, metabolomic platform, molecular biology facility, imaging facility, etc).

Finally, discussion with the different members of the unit led to the following points:

PhD and Postdocs: Very satisfied by the general spirit, atmosphere and mentoring support. Highly motivated and dedicated.

Technicians, Administrative staff and Engineers: Very positive general feeling. Some personnels mentioned the lack of possibility for promotion.

Researchers with permanent positions: emphasized the very positive atmosphere, possibility to interact and exchange material freely. This is a cohesive unit that gets along very well. Mentioned the fact that the teams were spread out in the building making it more difficult to interact and pointed out the need to recruit more personnel.

Assessment of the unit's involvement in training through research

1) 42 Ph.D. awarded during the 2007-2012 period (including the end of the year 2012)

2) 169 articles were published by Ph.D. students of the unit with an average of 4.0 articles/Ph.D. student (ranging from 1 to 9). The Ph.D. students were 1st authors in approximately half of the papers.

3) It is mandatory for unit's students to attend and present at the weekly seminar series both at the level of the unit and teams.

4) Scientific progress of PhD students is evaluated through the doctoral school. After 18 months, an independent committee composed of external PIs provides an assessement of the scientific project, the progress realized so far and recommendations.

As alluded in previously, training through research and unit's attractivity are reflected by the recruitment of students and post-doc fellows from many countries around the world and with many different educational backgrounds (basic sciences, medicine, pharmacy, engineering). The facts that post-docs and students are (i) very satisfied by the scientific support and atmosphere of the Unit and (ii) have all found employment after they left the unit confirm the quality of the training.

Assessment of the five-year plan and strategy

It is the point of view of the evaluation committee that so far the strategy (or apparent lack of strategy) governing the unit expansion and evolution has largely been based on opportunistic recruitment of Teams rather than being based on a specific strategic plan aligning research priorities with recruitment and resources.

The feasibility of the projects presented for the next five years is realistic. This is a global and coherent plan that addresses important basic issues such as cellular detection of and response to toxic and infectious agents as well as the molecular and cellular mechanisms leading to diseases such as neurological, metabolic, infectious and joint diseases. It takes advantage of the complementary expertise and synergy between the teams and collaborations with a large set of academic and non-academic partners. We have no doubt that numerous key discoveries resulting in high impact publications will be obtained.

Both the implementation of strategic recommendations (see § recommendations, section #2) as well as increased support from the two managing bodies should provide the Unit with an ideal environment to develop its scientific potential to the full extent.

4 • Team-by-team analysis

Team 1 : Toxicology Signaling and Metabolism

Name of team leader: Mr Xavier COUMOUL

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	10 (3,2)	9 (3,2)	9 (3,2)
N2: Permanent EPST or EPIC researchers and similar positions	4 (4)	3 (3)	3 (3)
N3: Other permanent staff (without research duties)	6 (3,7)	5 (2,9)	5 (2,9)
N4: Other professors (PREM, ECC, etc.)	1		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	1	1
N6: Other contractual staff (without research duties)	1 (0,2)	1 (0,2)	1 (0,2)
TOTAL N1 to N6	24	19	19

N3: technician staff (30/06/12: 1 IE, 1 IR, 1 AI, 1 TCH; 2014-: 1 IE, 1 IR, 1 TCH)

N6: includes 1 contractual agent (0,2 ETP)

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	11	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	12	10

Detailed assessments

Team 1 was created in January 2010 by the fusion of two groups from two different INSERM units, associating expertise in toxicology, metabolism, biochemistry and cell biology and works on a topic of interest for public health. The research activity of this team is mostly dedicated to the study of the toxicological effects of pollutants, mainly ligands of the Aryl hydrocarbon Receptor (AhR), a transcriptional factor involved in the regulation of the expression of many target genes as well as effects of alcohol.

Assessment of scientific quality and outputs

Toxicology is a competitive field. Whereas it is easy to see the important role played by Team 1 in the French context, it is more difficult to appreciate its impact at the european and international levels.

The research carried out by Team 1 can be qualified as quite good, although productivity is variable among researchers. Professors, assistant-professors and full-time researchers have produced 76 publications including12 reviews in peer-reviewed journals during the 2007-2012 period (not counting French publications). It is relevant to note that some major publications have been produced by some researchers before their arrival in Team 1. Among the 30 research publications with a member of the team as the first and/or the last author the most significant ones include 2 *Oncogene*, 1 *Cancer Research*, 2 *Environmental Health Perspectives*, 1 *Plos One*, to name a few.

In addition, clinicians have produced 105 international publications in various fields

The team leaders have been invited to speak at numerous scientific meetings including 19 internationally (out of 70).

Assessment of the unit's academic reputation and appeal

There is a real visibility of the team at the national level in the field of toxicology. Members of the team have many responsabilities in the field of toxicology in different national bodies but the international dimension is much less visible.

The project of the team is in adequation with the priorities elaborated by INSERM, Paris 5 University and different committees, associations or foundations. The team has set up many national initiatives in the field of toxicology with an excellent participation in the organization and life of numerous committees.

We note that many different funding sources have been obtained by the team leaders but all of them were at the local or national levels. Presently the team is not involved in european networks.

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

The research topic is really important in terms of public health.

The team, more specifically some members of the team, participate in many scientific committees and diverse audiences in the field of toxicology at the national level. Different forms of interaction between researchers and their environment are largely notified (contribution to guidelines, contribution to dissemination of scientific culture in their field…).

We also note the filing of two patents (one at the international level).

Assessment of the unit's organisation and life

The team leader plays an essential role in the team organization and life. The interactions between academic researchers and clinicians are mostly via one teacher-researcher (MCU-PH).

The clinicians do not participate to the weekly meetings of the team, likely because they are working in hospitals (G.Pompidou, Necker) that are not closely located. More interactions between academic researchers and clinicians are encouraged.

Assessment of the unit's involvement in training through research

There are many contributions in the teaching duties, mainly for three persons and in the field of toxicology with the responsability of several master programs, the organisation of different teaching units, the co-responsability for two global year-levels of university teaching (Licence 2 and 3) and the implementation of a new "Master of Toxicology".

Assessment of the five-year plan and strategy

In the continuity of the main projects of the Team, the results obtained during the last period generate for the five-year plan 4 lines of research which will be developed in a focused way:

1 – AhR, cancer progression and fibrosis

2 – AhR, adipose tissue and metabolism

3 – AhR and neurobehavioral effects

4 – Structural and functional plasticity of the AhR (in collaboration with team 4)

The proposed project, largely based on the work of the previous years, aims at characterizing novel effects of pollutants hijacking the AhR signaling. Using *in vitro, in vivo* and human complementary models and new methodological approaches, the team might be able to elucidate new mechanisms of toxicity, identify novel biomarkers and propose new toxicity tests.

Conclusion

- Strengths and opportunities:

The project is focusing on relevant public health priorities and Team 1 is recognized in this particular field at the national level and to some extent at the international level.

Some members of the Team are involved in numerous initiatives (scientific, political and cultural), positioning this team as a leading team in the field of toxicology.

- Weaknesses and threats:

The number of researchers is decreasing (professors and full time scientists) for the next period.

There are not a lot of PhD students by comparison with the number of supervisors (HDR): for example, on 30/06/2012, there were 4 PhD for 12 HDR but this is partly explained by the fact that clinicians do no act, for most of them, as PhD supervisors.

The international dimension is not visible enough (no european or international funding and not a lot of international communications).

- Recommendations:

The team leader should reduce whenever possible his time devoted to administrative tasks (e.g. various scientific committees and teaching-related activities).

The 4 project axes are of true interest but will be consuming in terms of ressources and personnel. To be more competitive, priorities and manpower for each axis should be carefully defined and allocated.

It is recommended to improve the visibility of the team at the international level. The group might benefit from more international interactions or collaborations with other groups involved in toxicology. Internal collaborations with other teams of unit 747 should also be considered and promoted.

Team 2 :

Pharmacology, Toxicology, and Cell Signalling of Cartilage and Intervertebral Disc

Name of team leader: Mr Francois RANNOU

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3 (1.1)	5 (2,2)	2 (1)
N2: Permanent EPST or EPIC researchers and similar positions	2	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.)			
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	7	8	3

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	4	4

• Detailed assessments

Assessment of scientific quality and outputs

This team emerged from a previous team whose expertise was chondrocyte biology and biochemistry. The present team leader is PUPH of Rehabilitation and therefore has emphasized translational research over the last years. The present team main interests are analysing cartilage and intervertebral disc degeneration during rheumatic diseases (mainly osteoarhtritis and acute joint inflammation) under mechanical, cytokinic and and/or oxidative stress in order to decipher pathophysiological molecular mechanisms and identify new therapeutic targets. They use in vitro mechanically strained chondrocytes cell culture models, and they master three animal models (mechanical model of osteoarthritis, an acute inflammation mouse model, and a mechanical model of scoliosis in the pig). For the past 5 years they have analysed the involvement of several signaling pathways that exhibited some chondroprotective effects including heme oxygenase and PLA2 inhibitors. Knowing that PPAR receptors alpha and gamma activation confer a preventive role against the inflammatory process, they used oxadiazolone derivatives as PPAR ligands, looking for a specific PPARgamma binder (collaboration with chemists from the CNRS and University of Tours). Using mRNA microarray of stretched chondrocytes, they also identified relaxin as a highly-mechanosensitive molecule potentiellially involved in matrix degradation. They are also involved in an innovative tissue engineering long-term research program aiming at the replacement of intervertebral disc using chitosan based biomaterial.

*During the 2007-2012 period, the team published 40 articles including 33 original articles in international journals. It includes publications in top-ranked journals in the field such as 3 in Annals of the Rheumathic Diseases (IF: 9.1), 4 in Arthritis Rheumatism (IF:8.4) 1 in J Immunology, etc.*Furthermore, fruitful collaborations related to molecules found to be involved in inflammation led to a significant number of articles in other research fields.

Assessment of the unit's academic reputation and appeal

The team leader is an elected member of the OARSI board, the international Society for osteoarthritis research and has chaired several meetings. The head of Team 2 has also been invited for lectures worldwide and is associate editor of two scientific international journals (*Plos One* and *Osteoarthritis and Cartilage*, leading journal in the field of osteoarthritis). Foreign students from several countries (including USA) have joined the team over the past five years.

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

The head of Team 2 has been repeatedly invited to give interviews in national or foreign newspapers and on TV. Team members are involved into general public education programs about joint diseases and osteoarthritis.

Assessment of the unit's organisation and life

Team members meet on a regular basis to share results and participate to the weekly meetings organised within the 747 unit. This allowed them to elaborate ongoing collaborations with two other teams of the unit (Teams 1 & 7). The team leader has taken the opportunity of his access to patients for initiating a biobank in inflammatory joint diseases and osteoarthritis.

Assessment of the unit's involvement in training through research

Students at the master level were trained and 5 PHD students have been recruited over the last 5 years, 2 of them having defended their thesis in 2007 and 2008. The three other PhD students (recruited in 2008 and 2009) should defend their thesis in the near future. One Professor and one Assistant Professor are involved in medical teaching. They propose the creation of an international master degree in biomedical engineering (to be evaluated) and their input are mainly at the level of the master degree.

Assessment of the five-year plan and strategy

The project is in the continuity with the previous one although with a higher concern about the therapeutics of osteoarthritis and arthritis and the recruitment of a PI working in the field of hypoxia. In this context, in addition to in vitro cell models, the team is developing in vivo animal models and strengthening the links with clinicians. Team 2 has developed strong collaborative projects with partners from both inside (potential anti-inflammatory effects of Arsenic, Team 7; involvement of the aryl hydrocarbon receptor in acute inflammation, Team 1) and outside (national and international) of the 747 Unit. The project is based on two work packages. WP1 is related to the regulation of inflammatory and oxidative stress in the acute phase of arthritis. First, the team will further extend the program on the anti-inflammatory properties of various oxadiazolone derivatives, the GIIAPLA2 inhibitors (via tight collaborations with chemists from two CNRS units of Tours University) using in vitro and in vivo models of joint inflammation. Second, a new project focusing on the involvement of cytosolic PCNA and HDAC1 in neutrophil survival has begun in collaboration with INSERM U1016, the final aim being to trigger neutrophil apoptosis in inflammatory joints. Third, the arrival of two new members with expertise in oxidative stress will give Team 2 the opportunity to analyse the effect of hypoxia and of the regulation of the thioredoxin/thioredoxin reductase-TXnipsystem in Normal and OA chondrocytes as well as in synoviocytes in the rheumatoid arthritis context. The second WP, is related to mechanical stress in joint and spine diseases. First, the team will carry on with the role and involvement of the mechanically-induced relaxin in cartilage destruction. Second, owing to the recruitment of a spine orthopaedic surgeon in the team, a model of scoliosis in the growing pig was developed in collaboration with VetagroSUP, Lyon which will allow them to analyse the changes in intervertebral disc chondrocyte phenotype at the cellular and molecular level.

A database from scoliotic patients, including both non invasive data and intervertebral disc samples, will be built up in parallel.

First, all together, the various work-packages planned by team 2 take their originality from the collaborations developed within the Unit (Arsenic project) and outside the team (role of neutrophils) while the general questions addressed are rather fundamental (ie signaling pathways and cells involved in joint destruction during acute and chronic inflammation). The second positive point is that they almost systematically include mechanical strain as a variable, a domain in which they have pioneered experimental procedures and acquired a well-known expertise. Third, the link with the patients via the team leader strengthened by the planning of translational projects such as the biobank and new animal models brings clinical relevance to the project. For these reasons, the specific projects developed here should allow the team to keep up with their international competitiveness. As for financing, the difficulties to obtain specific grants is underlined in the project. The collaborations with chemists could help to improve financing. An effort for widening the scope of collaborations with teams from other European countries may open strategic opportunities for participating to European calls. Finally, national translational research calls or university hospital clinical research calls (PHRC) might represent another potential source of financing which have not been enough exploited so far.

Conclusion

- Strengths and opportunities:

Mastering relevant and/or innovative animal models as well as strong relationships with the clinics has allowed Team 2 to put together a bank of human samples and a clinical database. Long term fruitful collaborations and skills to develop new ones.

- Weaknesses and threats:

Despite the fact that new members will be recruited, the number of projects remains somehow too high, considering that there is no full time researchers in this team and that the members are strongly involved in teaching and/or patient care. As an example, the synoviocyte project, although relevant, may over broaden the scope of the team. On the other hand, the drug development project is not connected to any pharma group, although the team got a grant from MSD (2010-12). The oxadiazolone derivatives are patented for a while and compounds from pharmas' library could have been screened on specific models set up by the group. Strategic choices leading to prioritization of the most promising projects may be needed to keep the team focused on its key expertises.

- Recommendations:

A genetic mouse model of relaxin invalidation or overexpression should be rapidly considered if in vitro data confirm the potential role of this molecule in joint destruction.

Team 3 : Mitochondrial disorders : pharmacological therapy and metabolic signaling

Name of team leader: Mr Jean BASTIN and Ms Fatima DJOUADI

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions		2 (0,5)	
N2: Permanent EPST or EPIC researchers and similar positions	2	2	2
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	
N6: Other contractual staff (without research duties)	1		
TOTAL N1 to N6	3	5 (0.5)	2

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2	
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	2	3

• Detailed assessments

Assessment of scientific quality and outputs

Team 3 research activities aim to identify and propose efficient therapeutic strategies that target mitochondrial metabolism (fatty acid oxidation, respiratory chain,…) in order to pharmacologically correct rare inborn mitochondrial diseases. This strategy goes from human cells (obtained through collaborations with genetic reference centers all over EU) to clinical studies in collaboration with physicians. Until recently, these pathologies with severe pediatric presentations and high mortality rates, were almost in a therapeutic impasse. Gene therapy was the only envisioned, but highly challenging, strategy. Considering that a significant proportion of patients affected by inherited mitochondrial disorders (IMD) still display a residual activity for fatty acid oxidation enzymes and/or respiratory chain complexes and taking advantage of animal studies that recently brought new knowlegde regarding signaling pathways controlling mitochondrial functions, Team 3 explored the ability of drugs targeting these pathways to correct mitochondrial disorders. The know-how of the team developed over the last years to manage comprehensive assessment of mitochondrial function and the collection of cells from patients allow Team 3 to be successful in this strategy. Notably, Team 3 showed in human fibroblats from patients that, bezafibrate, an agonist of PPAR, was able to correct both VLCAD deficiency (*Am J Human Genetics* 2007; *Biochimica Biophysica Acta* 2010) and respirarory chain disorders (*J Clin Endoc Metab* 2008). They also demonstrated that bezafibrate efficiently stimulates residual enzyme activity in cells from patients with Carnitine Palmitoyl Transferase 2 (CPT2) deficiency (*Human Mol Genetics* 2005, JCEM 2005, *J Inherited Metabolic Disease*, 2008). This was the first *in vitro* evidence of the efficiency of a pharmacological approach in the treatment of a fatty acid oxidation disorder. In collaboration with physicians from Necker hospital, this led Team 3 to set-up a clinical study. In patients with the muscular form of CPT2 deficiency, they demonstrated that bezafibrate administration efficiently corrects CPT2-deficiency. Enrolled patients reported an improvement in exercise tolerance, a decline in the intensity and the duration of pain, along with a decrease in rhabdomyloysis episodes (*NEJM* 2009, *Clin Pharmacol Ther*, 2010). Team 3 recently extended this strategy to resveratrol (RSV) (proposed as a sirtuin 1 agonist in mice) and showed *in vitro* that RSV is able to correct VLCAD deficiency as well as deficit in respiratory chain complexes (HMG 2011). The set-up strategy is this very comprehensive and translational. Scientific quality is very good with respect to the size of the group. The team published 15 papers in peer-reviewed journals. One third (6 papers) of the articles have an impact factor (IF) between 5 and 10, and one third (5 articles) an IF beyond 10. Notably, the team published as main authors 2 papers in the *American Journal of Human Genetics* (IF 10,6), 2 in *Cell Metabolism* (IF 13,6) and one in the *New England Journal of Medecine* (IF 53,3). **As a conclusion, the scientific quality and achievements of team 3 are excellent.**

Assessment of the unit's academic reputation and appeal

Recent publications in high ranking journals significantly increased the visibility of the team, which was already known in the field. The team works in close collaboration with physicians and reference centers for genetic diseases at different places worldwide (UK, Denmark, Japan, The Netherlands, Australia, Canada).They are regularly contacted by physicians over the world in order to help them assess bezafibrate responsiveness of their patient cells. Over the last years, the PIs of team 3 have been invited to, and attended several conferences and workshops in the field (in France, EU and US). The number of invitations and talks is modest (10) but might be related to the limited number of conferences in the field. The PIs of Team 3 belong to scientific societies at the national level and are involved in networks in the field. They review grants and projects from differents entities on a regular basis (ANR, AFM, Welcome Trust, Prinses Beatrix Funds,…). They are also peer-reviewers for various journals in the field (Journal of Inherited Diseases, Clinical Genetics, BBA Molecular Basis of Diseases,…). Team 3 receives funds from ANR, AFM and ELA (Team 3 PIs are PIs for these projects). Noteworthy, Team 3 works in close collaboration with AFM to set-up a large controlled clinical trial for bezafibrate in CPT2 and VLCAD deficient patients. It should be pointed out that the recruitment of graduate students (PhD students) is quite low. Team 3 should consolidate it in order to maintain their competitivity in the field. To conclude, academic reputation and appeal of team 3 is good.

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

The oustanding work of Team 3 on bezafibrate for the treatment of CPT-2 deficiency in patients (NEJM, 2009) brought new perspectives for the treatment of IMD. This has been highlighted by several medias (press release from the AFM, TV report "Le magazine de la Santé", France 5, Feb 2009; Vaincre les myopathies, May-June 2009). This work allows physicians and pharma companies to revisite their view of rare mitochondrial diseases treatment since the pharmacological approach with bezafibrate clearly improves the quality of life of CPT2-deficient patients. This allowed Team 3 to increase their interactions with pharma companies (Roche, GSK and Genfit) and provided them with research funds, salaries for technician and phD students (CIFRE grant with GSK) and proprietary compounds (assessment of AMPK activators). Overall, interaction with social, economic and cultural environment is really good.

Assessment of the unit's organisation and life

Over the last years, the size of Team 3 was small (2 PIs (full time scientist: researcher INSERM, 1 technician (non permanent position), 1 graduate student). The team recently grew up with the recruitement of a post-doctoral fellow, 2 people from the biochemistry department of Necker hospital and 1 full professor from Necker hospital, head of the center for clinical investigation although with quite a low level of presence in the group due to hospital duties. Noteworthy, Team 3 should reinforce its task force by the hiring of a junior full-time scientist and a technician (the current technician does not have a permanent position). To conclude, prospects regarding team 3 organization and life are good despite its small size which could be considered as a weakness in this competitive field.

Assessment of the unit's involvement in training through research

The level of training through research is quite low. Over the last 5 years only 1 phD student has been trained. Several master students have been trained (7). One post-doc fellow was recently hired. PIs participate to master programs in their field (University Paris Diderot, University of Burgundy). The involvement of Team 3 in training should increase in the near future.

Assessment of the five-year plan and strategy

During the next 5 years, Team 3 will maintain its focus on the pharmacological treatment of IMD with a translational strategy. Recent investigations in the field of energy metabolism unravelled a key role of the AMPK-SIRT1-PGC1 signaling pathway in the control of the mitochondrial function. So far, neither this pathway, nor the contribution of the 7 sirtuins members, have been investigated in the context of IMD, especially in humans. The project proposed by Team 3 is promising since these pathways are of great interest for many pharma companies. Team 3 has several advantages in the field. First, this team has a longstanding expertise in the comprehensive assessment of mitochondrial function. Second, contrary to many research groups currently working in this field (sirtuin, AMPK, PCG1), Team 3 does not use rodent but human material. The work of Team 3 will be instrumental to assess the efficiency of AMPK-SIRT-PGC1 activators in humans. Third, Team 3 has tight connections with physicians and european reference centers for genetic diseases. Nevertheless, Team 3 should keep in mind that their work on bezafibrate shed lights on new therapeutic opportunities for genetic mitochondrial diseases. A continuously growing number of highly competitive academic and pharma groups in the field of energy metabolism are now being interested in IMD. In order to maintain its competitivity, Team 3 has to develop a medium-to-high throughput strategy. In a first attempt, Team 3 should also focus on drugs already used clinically, such as biguanides, or on natural compounds (such as RSV), as these drugs are already authorized for other applications in human clinic. This should allow Team 3 to move faster into clinical trials. Overall, the 5 years strategy of team 3 is good although one may have expected a strategy to establish closer links with pharma groups.

Conclusion

- Strengths and opportunities:

The strategy conducted by Team 3 over the past years is highly comprehensive and translational. Team 3 is among the few basic research teams worlwide that can claim that their work was truly translated into therapeutic applications and in improved patient health. Team 3 has a longstanding expertise in the comprehensive assessment of mitochondrial function. Contrary to many research groups currently working in this field, team 3 does not use rodent but human models. They have tight connections with physicians and european reference centers for genetic diseases. Team 3 visibility has significantly increased over the past years thanks to publications in high ranking journals. This allowed Team 3 to set-up collaborations with a few pharma companies.

- Weaknesses and threats:

Over the past years, the size of team 3 was small. The team recently grew up as aforementioned. This will reinforce the strengths of team 3 in terms of research and potentially attractiveness for medical students. However, the PIs of Team 3 have to actively work for a good and quick integration of these new members in order to efficiently translate these recruitments into high ranking publications, development of new know-hows (metabolomics and HTS) and novel clinical perspectives for the treatment of mitochondrial diseases. With their clinical study with bezafibrate, Team 3 has generated its own competition. A continuously growing number of highly competitive academic and pharma groups are now starting to be interested in IMD.

- Recommendations:

Human resources

Even if recently reinforced, Team 3 should still increase and stabilize its task force by the hiring of a junior full-time scientist and a technician (the current technician does not have a permanent position).This is a key point since the competition is continuously growing in the field.Team 3 needs to stabilize the number of permanent positions in order to maintain scientific and technological advantages in the field.

Scientific strategy

A growing number of highly competitive academic groups are being interested in IMD. In order to maintain its competitivity, Team 3 should develop medium-to-high throughput screening (HTS) strategy. This project, as well as the development of new strategies for the assessment of the mitochondrial function based on metabolomic approches should be priorities for the new team members.

Team 3 should focus on drugs already used clinically as well as on natural compounds. The former could be quickly tested in the context of clinical studies. With regards to the in vitro data obtained with resveratrol (RSV), Team 3 should consider conducting a clinical study with RSV. Several human studies performed in healthy and obese subjects for various durations (4 to 12 weeks) demonstrated that RSV is well tolerated (Timmers S, et al Cell Metab, 2011; Poulsen MM, et al Diabetes. 2012; Yoshino J et al Cell Metab, 2012). Team 3 should also consider to increase the valorization of their work and their expertise by patent filing and by developing proprietary screening strategies or fee-for-service activities.

Industrial partnerships

It might be worth increasing Team 3 partnerships with pharma companies which would help them to raise funds and to have access to more compounds.

Team 4 : Pharmacotoxicology and Structural Biology

Name of team leader: Mr Pierre NIOCHE

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions			
N2: Permanent EPST or EPIC researchers and similar positions	1	1	1
N3: Other permanent staff (without research duties)	1	2	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	1	1
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	4	4	2

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students		
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	0	1

• Detailed assessments

Assessment of scientific quality and outputs

This team started its activity in September 2006 with a "Contrat Avenir INSERM" obtained by the team leader. It has acquired expertise in structural biology techniques and developed three projects corresponding to three protein targets involved in xenobiotic metabolism or mechanism of action, namely soluble Guanylate cyclase (sGC), cytochrome P450 and Aryl Hydrocarbon Receptor (AhR). The team is still young and was small over the last 4 years (3 people: the PI, a Post-doc and a technician).

The team has received several grants (AVENIR, NIH, CODDIM equipment, ANR…) which should cover expenses up until 2015.

The scientific production of the team during the 2007-2012 period is moderate, but in journals with high or sometimes the highest impact factors: one original publication in Nature in 2008 (PI first co-author) and one in ACS Chem Biol (IF 6.44, where the PI is the 4th author) in 2012. Since the PI integrated INSERM in 2006, he published 3 other papers. In addition, a manuscript is in revision in Nature. This rather slow production is thus explained by the small team size and above all their strong will to publish in outstanding journals, which may be encouraged to a certain extent.

The team has also been able to obtain many results that have not been published yet, demonstrating a good scientific activity.

Assessment of the unit's academic reputation and appeal

This young team is not yet well known. However, the PI was invited to give two talks in France during the evaluation period, one in an academic and one in an industrial settings. Also, the team has apparently been able to attract a study engineer (IE) for the next period (provided permission is granted for his moving by INSERM).

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

The team obtained a contract with a biotech company.

In addition, the team lab technician is an entomologist who recently authored a book on the therapeutic uses of insects, for which he was invited by different media (including national TV and radio shows).

Assessment of the unit's organisation and life

Being comprised of only 3 persons and a few students, the team management is probably rather straightforward. The PI supervises the three research projects and the other persons (including a PhD student) each work on a single project. However, the team policy about decision making and meetings is not presented in the documents.

Assessment of the unit's involvement in training through research

Owing to its small size, the team has a good involvement in training to and through reseach, as they have hosted 2 post-docs, 1 PhD student, 4 master-2, 4 master-1, as well as BTS (license level) students.

Also, the PI is in charge of a teaching module at master-1 level, and gives lessons at license, master-1 and master-2 levels, in biochemistry and physics (75h/year). The post-doc also gives a few hours' lessons at the license level.

The PI intends to defend his HDR (habilitation to supervize PhD students) soon (the document is apparently ready).

Assessment of the five-year plan and strategy

The projects are in direct continuity with the research programs carried out over the last six years and tend to be more autonomous from the Texan team with which the PI worked during his post-doc and still published lately. Pursuing three different projects for a team of 3-4 members may seem quite ambitious, but it may be a way to minimize the risks of dead-end research. These projects are of high scientific importance and seem to be feasible owing to the results already obtained by the team, including some preliminary results for the new axis on AhR.

Altogether, as the PI stated this is still a "high-risk, high-reward" strategy that is perfectly understandable, provided it gives rise to more published papers, even if reporting negative results.

Conclusion

Strengths and opportunities:

- The group leader and his team have addressed the important question of the structure-function relationships of three proteins involved in the metabolism of xenobiotics.
- They have acquired a great experience in structural biochemistry and developed a protein production/ crystallography platform.
- They have close collaboration with an American team working in the same domain.
- One of the recent lines of research has been developed in close collaboration with Team 1 (for which they obtained an ANR grant in common).
- The team had one paper in Nature in the previous period, and has one in revision in the same journal.
- They could recently purchase the equipments for protein production and crytallography.
- They have many results to be published.
- One engineer and one teacher-researcher may join within two years.

Weaknesses and threats:

- The team strategy to publish in high profile journals only has seriously limited the number of published papers since 2007.
- Another weakness is the limited size of the team compared with the number of projects proposed.
- Nobody in the team is habilitated to mentor PhD students (HDR).

Recommendations:

- The PI is a highly promising group leader who has managed to develop his own original project in an important and incompletely explored field of research.
- Some of the many results already obtained must be rapidly submitted for publication, as not all may deserve the highest ranking journals. The ability of the team to publish on their own must be demonstrated.
- The staff of this small team has to be reinforced if they want to push their three projects forward.
- The project on AhR, although the latest, is probably the most coherent with the unit's main thematics, as well as the most original, and might be priviledged over the other two if the team have to restrain their scope.
- The committee also recommends that the team leader presents his HDR as soon as possible.

Team 5 : Stem cells, signaling and prions

Name of team leader: Ms Odile KELLERMANN / Mr Benoît SCHNEIDER

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2 (1)	2 (1)	2 (1)
N2: Permanent EPST or EPIC researchers and similar positions	3	1	1
N3: Other permanent staff (without research duties)	1	1	
N4: Other professors (PREM, ECC, etc.)	1	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1	1
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	8	6	5

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	7	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	4	3

• Detailed assessments

Assessment of scientific quality and outputs

In 2008, Team 5 moved from the CNRS campus located in Villejuif to the University Paris Descartes and joined the INSERM Unit UMR-S747. For the 2014-2019 period, Team 5 will split into two distinct entities Team 5 and Team 6.

Team 5 follows 3 main axis of research:

1.miRNA: The group has demonstrated that miR-16 behaves as a "micromanager" in the action of serotonin receptor inhibitor (SRI) antidepressants as published in several high profile papers (*Science* 2010; *Transl. Psy*. 2011; *Curr. Op. Neurobiol*. 2011). This research line will mostly be carried out in the future by Team 6 which is emerging from Team 5.

2. Prion and neurodegenerative diseases : The group has been studying the multifaceted role of the cellular prion protein (PrP_c) ion neurons. The data on this topic has been published in several papers (*Cell Signal* 2008; *J. Neurochem*. 2009; *PLoS One* 2009; *Faseb J*. 2012). The Team will continue to work on the projects within this axis and will explore how the pathogenic prions (PrP_sc) deviate PrP_c signalling and alter neuronal functional in relation to the Alzheimer disease. On this topic there is a bulk of experimental data already published (*J Biol Chem*, 2008; *Cell Death&Dis*, 2013) and one paper under revision at *Nat. Medicine*. There are also many preliminary data which indicates the high quality and clear potential for scientific advancement in the field. However, decreased interest in the prion disease itself and limited funding for this topic makes it warranted to direct the research more towards the Alzheimer disease.

3. Mineralized tissue. The group has been exploring how 5-HT_2B_R contributes to normal and ectopic calcification (*Cell Signal* 2006; *J Biol Chem* submitted). In addition, a substantial emphasis is also placed on identification of odontogenic stem cell identity and dental repair (*Adv. J. Detal. Res* 2011; *Eur. J. Oral Sci*, 2011; *Eur Cell Mater* 2012).

Overall, the scientific quality is very good. The productivity is very high with 40 publications in 2008-2013. Several studies have been published in top-ranked journals such as *Science* (2010); *Transl. Psy*. (2011); *Curr. Op. Neurobiol.* (2011) and *FASEB J* (2012).

Assessment of the unit's academic reputation and appeal

The good scientific reputation of the team 5 is reflected in "Highlights" and "News" published in several top journal regarding their discovery of new mechanisms of regulation of anti-depressant drugs (Nat Rev. Neuroscience, 2010; Nat. Med, 2010). In addition, the national standing of the team is revealed by invited reviews in INSERM Science et Sante, 2011 and INSERM Decouverte 2012.

The fact that 70% of financial support of the team 5 is coming from ANR for 3 different projects (miRNA, PrP signals, Prions & SensiTNF) together with several fellowships indicate the high scientific quality and reputation of the team.

The team has several on-going national and international collaborations (9 and 7, respectively) on different topics which are included on the research program and will be further developed in coming years.

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

The team has good social interaction with the environment which is reflected by invitation of members of group to be interviewed by various media (on the mode of action of Prozac; on Mercury- and Bisphenol A- associated toxicities in dentistry) and participated to public discussion ("Quotidien du Médecin", INSERM Santé). Team members participate also in numerous meetings.

The Team is collaborating with several companies including Hoffmann-La Roche, UsefulProgress and SEPTODONT.

The team members are serving as experts in several scientific committees including the MESR/CNRS board section 23/INSERM Avenir/INRA; the French Committee of Transmissible Spongiform Encephalopathy (ANSES, French food Safety Agency since 2004); the ANR; act as coordinator of Interface INSERM-Odontology, member of Board of International Association for Dental Research, expert for international grants (Canada, US, Italy...) and for AFSSAPS.

Some of the team members are also involved in editing activity such as as managing editor for *Frontiers in Bioscience* (2010-2011) and is academic editor for *PLoS One* (2011-). Another member is editor for Frontiers between science and clinical Odontology, Coxmore 2009 and Bentham e-book 2010-2012.

Assessment of the unit's organisation and life

The Team consists of 6 permanent members, 4 posdoctoral fellows and 4 PhD students. The Team is well organized but the measures needs to be taken so that the spin off Team 6 will get opportunity to develop as independent group in the future.

Assessment of the unit's involvement in training through research

Most members of Team 5 are involved in teaching duties in several programs of University Paris V (Master of Biomedical Engineering; first year of medical school) as well as other institutions such as "Agrégation des Sciences de la Vie" and Biology Courses at Ecole Polytechnique. 8 members of the team are engaged as PhD "moniteurs/assistants.

Assessment of the five-year plan and strategy

In coming years Team 5 plans to continue research in the areas where they have strong reputation and well-established methodology and technology but at the same time explore new avenues within this topics. In particular, the Team plans to explore:

1. How do pathogenic prions disrupt neuronal polarity in relation with the functional role of the cellular prion protein (PrPC) in neuronal differentiation. As it was demonstrated in the 1C11 cell line, the lack of PrP_c leads to defect in the acquisition of neuronal polarity and impairment of neurotransmitter-associated functions which is mediated by overactivity of Rho kinase. The Team aims to investigate how the manipulation with Rho kinases activity will influence cellular abnormalities in prion-infected cells.

2. What is the mechanism by which PrP_sc or amyloid Abeta peptides interfere with PrP_c-dependent signaling and promote PDK1 overactivation. It has been shown by the Team that antagonizing PDK1 overactivity alleviates prion and Alzheimer's diseases and therefore, studying the mechanisms controlling PDK1 activity at the biochemical level is of big scientific and clinical importance.

3. Whether the 1C11 cell line can provide a new experimental paradigm for neurotoxicology studies . It has been shown that manufactured nanoparticles affect the self-renewal and the neuronal differentiation potential of 1C11 cells. The team aims that assessment of the nanoparticle-associated neurotoxicity could provide clues as to mechanisms of neuronal differentiation and homeostasis.

4. What are the hallmarks defining the identity of dental-pulp stem cells. With perspective of cell therapies for tooth repair, it is necessary to identify markers allowing the localization and isolation of odontogenic stem cells and to characterize signals promoting their recruitment.

The proposed work is well planned and all work is carefully designed. The projects related to the prion disease and PrP are solid and sound, with high scientific level and based on the previous publications and well-established approaches. The dental pulp-related projects are not closely integrated with the rest of the proposal and lack the vision for further development. The risk of overlap on mir16 –related projects with team 6. should be avoided.

Conclusion

 Strengths and opportunities:

The work according to applicants is benefited from lineage precursor cell lines, which can be expanded as immature progenitors and by creating appropriate conditions differentiate into mature neuronal phenotype. A long-lasting and fruitful collaboration with J-M. Launay (Hôpital Lariboisière, Paris & Hoffmann LaRoche, Basel, Switzerland) can be also considered as strength.

The publications in top-ranked journals (*Science* 2000 & 2010; *PNAS* 2003; *Transl. Psy.* 2011; *Curr. Op. Neurobiol.* 2011) is reflecting the strength and high scientific level of the group. Also, additional funding attracted by the group is strength. The possibility to acquire the P3 laboratory in the Centre Universitaire des Saints-Pères for prion studies represents a clear opportunity for further development of prion-related projects.

 Weaknesses and threats:

The lack of P3 facilities available for prion studies in the University Paris Descartes, which forces Team 5 to carry out experiments in distant laboratories (INRA Jouy-en-Josas).Despite multiple attempts, Team 5 has not yet succeeded in obtaining European funding. Furthermore, more and more limited financial resources from ANR or national foundations (notably on the prion topic) could threaten the research activity.The initiation of the project regarding Alzheimer's disease without prior experience and very high competition in the field is clearly threat.The use of the only one cell line in the research is certainly a weakness. and in addition the work related to the tooth stem cells/progenitors is not logically incorporated in the overall project/research line of the group.

 Recommendations:

1. To use more than one cell line in the work and verify data more extensively with primary cells and in vivo models.
2. Avoid use of the stem cells as the main topic of the research because it is not clear how the stem cell research is linked to the projects carried by the group. In most cases there is immortalized cell line or progenitor/precursor cells (in case of tooth) and there is no clear vision how this research line should be continued and translated in the clinical settings.

Team 6 : Signaling and neurological pathophysiology

Name of team leader: Ms Sophie MOUILLET-RICHARD

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions			
N2: Permanent EPST or EPIC researchers and similar positions		2	2
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	
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6		3	2

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		1

• Detailed assessments

Assessment of scientific quality and outputs

The team arises from Team 5 "stem cells, signaling and prions" with a view to develop specifically projects centered on two axis: "microRNAs and depression" and "prion protein signaling". It is based on the expertise gained by two permanent full-time staff (2 CR1 inserm) on the pathophysiology of neuronal cells and cell signaling studies.

The scientific quality of Team 6 is good. It will be separated from the Team 5 and expected to develop as independent Team. The previous track record is good and proposed project is also and up-to-date.

The publication record of Team 6 members (during the 2007-2012 period when part of Team 5) comprises 17 articles most of which ranked Q1, including 1 *Science*, 1 *Current Opinion in Neurobiology*, 1 *Neurobiology of Disease*, 1 *FASEB* J, 2 *Journal of Biological Chemistry*, 1 *Translational Psychiatry*.

Assessment of the unit's academic reputation and appeal

It is difficult to assess the academic appeal since this is newly formed Team. However, the Team certainly has the potential to develop into academically attractive and appealing one. Team members are part of international and national scientific societies, and are involved also in international collaborations. Team members are participating in journal reviewing activities as well they are part of several evaluation committees.

More precisely, members of Team 6 are involved in international societies such as the ASBMB (American Society for Biochem. and Mol. Biology) and the SFBBM (Société Française de Biochimie et Biologie Moléculaire).

Several national and international collaborations (3 and 4, respectively) also speaks in favour of team's academic reputation.

The team leader served as Managing Editor for Frontiers in Bioscience with 6 reviews on "*Cellular prion protein partners and signaling*" (2010-2011). She is also currently serving as Academic Editor for *PLoS One*. She has been invited as speaker at European Congress Neuropsychopharmacology workshop for young scientists (Nice 2012). The Team members are reviewing for diverse journals (*JBC, PLoS One, FEBS Letters, Neurobiol. Dis, Mol. Neurodegen*, etc) as well as granting agencies (ANSES) and PhD programs and master juries.

The team will benefit from interactions with team 5 and an ongoing collaboration with JM Launay (Hopital Lariboissière) and Hoffmann-LaRoche.

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

The members of Team 6 are engaged in several teaching activity such as Master in Biomedical Engineering (BME, Paris V); Monitorat Ecole Polytechnique; Monitorat Ecole Polytechnique. The Team leader's position is only researcher and does not include obligation to teach.

Assessment of the unit's organisation and life

Not applicable.

Assessment of the unit's involvement in training through research

This is probably not sufficient for the established team but for this young team this might be good starting point. However, team needs to do much work in order to obtain funding and attract young researchers at PhD and postdoc level.

Assessment of the five-year plan and strategy

The main research questions raised in the proposed work is triggered/initiated by the previous work showing the role of microRNA in the depression-treatment through the use of serotonin reuptake inhibitors (SRI). Based on previous work, in upcoming period the group will address the following issues:

1. what are the signaling pathways orchestrating the response of serotonergic or noradrenergic neurons to SRI antidepressants.

2. what is the relevance of the S100beta/miR-15/miR-16 cascade to the dysfunction of noradrenergic neurons in AD.
3. Can we gain insight into the neuroprotective function imparted by the cellular prion protein.
4. what is the role exerted by PrP_c in the biology of normal and cancer stem cells.

The strategy and plan is solid and scientific sound. It builds on team leaders' previous findings in respect to miR-16 and serotoninergic system but also introduces new topics such as prion proteins and cancer stem cells. Since it is a new Team, it might be wiser to keep working on well-established research lines and be more careful with introduction of new and very competitive research topics. In addition, Team 6 should not relay so heavily on 1C11 cell line and diversify in vitro system. Finally, additional in vivo studies especially utilizing transgenic animals for validating in vitro studies are highly warranted.

Conclusion

Strengths and opportunities:

Team 6 has a strong experience in work related to the field of prion and microRNAs and depression. The contribution of the Team at international level is acknowledged by the invitation to edit Frontiers in Bioscience, several invited reviews, and invited talks at international meetings.The strength of the team is also evident from very good previous period publication record of the team members which includes 17 articles in good to excellent journals such as Science, Current Opinion in Neurobiology, Neurobiology of Disease, FASEB Journal and Journal of Biological Chemistry. The opportunity of the team to continue collaboration with Team 5 is certainly an added value as well as ongoing collaboration with JM Launay (Hôpital Lariboisière) and Hoffmann-LaRoche. Some novel preliminary data are also creating good opportunity to obtain additional findings.

Weaknesses and threats:

The major weakness is linked with the fact that it is a newly formed Team and it has not yet secured additional funding. The topic of the research is also very competitive and Team 6 does not have any track record in cancer stem cells field. It will be difficult to attract external funding especially European funding. Another weakness is that Team 6 is mostly concentrating the work on single cell line 1C11 which might be drawback and in some cases not the optimal system, especially when it comes to PrP related work. Finally, the opportunity to split the present Team 5 into two independent teams (i.e. 5&6) remains questionable and the committee wondered whether it would have been wiser for the head of Team 6 to remain few more years within Team 5 structure in order to develop successfully her two axis of research and confirm her scientific independance.

Recommendations:

1. Concentrate initially on well-established research lines with higher probability of production and publication of high quality papers which will help to attract much needed external funding. With additional funding, extend the research towards more topics and new projects.
2. Diversify research by including other cell lines and primary cells.
3. More extensively validate data using *in vivo* models.
4. Get involved in more international and national collaborations to increase publication record.
5. Get involved in more teaching activity and attract master and undergraduate students to increase work power.

Team 7 : Mechanism of interferon action and biotherapeutic pathways

Name of team leader: Ms Mounira CHELBI-ALIX and Mr Sebastien NISOLE

Workforce

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions			
N2: Permanent researchers from Institutions and similar positions	3	3	3
N3: Other permanent staff (without research duties)			
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)			
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	2	2	2
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	5	5	5

Percentage of producers	***100 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	8	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit*	0	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

This Team is interested in the mechanisms that regulate interferon antiviral mechanisms using the promyelocytic tumor suppressor (PML) and other members of the TRIM family as experimetal tools. This research area has significance for the understanding of the mechanisms that regulate innate viral immunity, inflammatory pathways and autoimmune disorders. The research output of this team has been first rate. The team senior leader is a recognized international leader in this field. She has worked in this subject for the last 25 years publishing 66 publications listed in pubmed. Many of these publications are in very reputable journals such as *Journal of Virology* (the leading journal in the field of virology). This is a remarkable and constistent track record. Notably, she has worked in the 1990s (and published several manuscripts) in the INSERM unit led by Mr. Hugues DE THÉ, a leader in the PML field. Therefore, she has excellent credentials and track record in this research area. The team has a junior co-leader. He has authored 23 publications listed in Pubmed. However, his publication record is limited since he has published only 2 experimental manuscripts as a senior author (*PLoS One* and *Retrovirology*).

Period under examination: 2007-2012. This team has used molecular, cellular and proteomics techniques to determine the role of PML in antiviral defence. The following are the most notable discoveries published in peer-reviewed journals: 1. PML confers resistance to rabies and encephalomyocarditis virus; 2. TRIM alpha and TRIM Y play a role in interferon induced antiretroviral activities; 3. The team confirmed that the RNF4 ubiquitin E3 ligase promotes the degradation of PML in cells treated with arsenic trioxide (this is one of the drugs of choice for the treatment of acute promyelocytic leukemia); 4. SUMOylation promotes the degradation of PML in cells infected by ECMV; 5. PML positively regulates interferon gamma signaling; 6. the team generated a novel proteomics approach to identify SUMOylated proteins. This method has greatly facilitated the task of identify SUMOylated proteins in cellular lysates and has been adopted by several laboratories around the world. Thus, this method is a signficant technological advancement in the field of proteomics.

The senior leader reported that she published 15 publications (4 reviews) and the junior leader 8 publications (1 review) during the period under consideration. The publications are mostly published as first authors in the best journals in the field of investigation of this team (J Virol 2010, 2010, 2011; J Biol Chem 2009; Mol Cell Proteomics 2011. However the team has not published in journals of the highest general impact such as Cell, Science or Nature. Therefore, the publication output from the team is very good, but not stellar.

This team has shown excellent productivity in producing research that can be translated into clinical applications (1 european patent, 1 canadian patent and 2 USA patents). These pertain to the use of arsenic trioxide in the treatment of autoimmune diseases and 3 of the patents have been licensed to the company MEDSENIC. Notably, we were informed during the on site visit, that a phase II clinical trial to assess the effect of arsenic trioxide in patients with lupus is ongoing and a phase II trial in graft versus host disease is planned for this year. This is an impressive achievement because it is rare for an academic team to bring its findings to clinical fruition.

In conclusion, this is a team that has achieved a very good output both in terms of discoveries and in terms of publication record. Its findings are published in the best journal in its field. More importantly, the applicability of the research performed is outstanding as demonstrated by the ongoing clinical trial. Moreover, the team's novel method to identify SUMOylated proteins has gained general acceptance and is being used by several laboratories around the world.

Assessment of the unit's academic reputation and appeal

The senior leader is well-known in the PML and interferon field internationally. French and international scientists of good quality are recruited and mantained. The team has active collaborations locally, nationally and internationally. In addition, this team has brought to clinical testing its discoveries. The team has also obtained funding from french agencies and a private source. The group has edited a special edition of Biochemie to celebrate the 50th anniversry of Interferon discovery, organized three scientific meetings on interferon biology (in Paris, Montreal and in Prato-Italy-), presented its work at 9 conferences. The group has several collaboratotions locally (INSERM unit 747 with Teams 2 and 9), nationally and internationally. The group had and has several post-doctoral fellows and Ph. D students, some of which are not French nationals.

Thus, the team's tools, methods and theoretical framework have a high degree of significance for the potential improvement of inflammatory human diseases. This led to excellent national and international visibility, appeal and reputation.

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

The discovery of the beneficial effects of arsenic trioxide in auto-immune and inflammatory diseases led to several reports in the lay press and on national television. The team obtained financial support from a private company for the development of arsenic trioxide therapy in autoimmune diseases.

Assessment of the unit's organisation and life

The unit is led by a senior and a junior leader. The team consists also of a researcher and an honorary researchers, 2 post-docs, 3 Ph. D. students and 2 master students. The team appears well balanced in its composition. The arrangement of having a junior leader may be instrumental in providing continuity upon the senior leader retirement, which is planned in 5-6 years. The morale is high and there are no apparent interpersonal conflicts. The team voiced the need for a technician to provide organizational and technical support.

Assessment of the unit's involvement in training through research

Degrees awarded since 2007: 3 Ph.D theses, 1 engineer degree, 2 masters I and 3 masters II. The Ph.D students that graduated published their research as first authors. This output appears excellent for a team of this size.

Assessment of the five-year plan and strategy

The team presented 3 main projects: 1. Study of the TRIM proteins in innate immunity; 2 study of the role of SUMO in regulating Interferon responses; and 3. to study the role of SUMO proteins in regulating antiviral defense.

The team proposed to use molecular and cellular biology techniques.The projects appeared to be coherent, complementary and are based on existing expertise and original data. The projects tackle original and novel questions relevant to the field of virology, cancer biology and innate immunity. Therefore, the research plan is well selected and likely to bring new knowledge.

Conclusion

 Strengths and opportunities:

This research team is first rate and has consistently produced novel findings in the field of virology, innate immunity, cancer biology publishing in leading journals in the field, producing several patents and a phase II clinical trial. The team leaders have made the decision to expand their studies to the analysis of all members of the TRIM family. The strenghts of this team are based on the experience of the senior leader, the existence of well established techniques to tackle the proposed research projects. The team is also collaborating with Team 2 and 9 and appears to nicely complement existing expertise in INSERM unit 737. This framework appears to be conducive to the generation of new knowledge regarding innate immunity, cancer biology and provides the promise to generate new therapies.

 Weaknesses and threats:

The arrangement of having a junior leader that could take the lead in 5-6 years time is wise. However, the committee has noted that the junior leader has a limited productivity as a senior author during the period under review. The junior leader authored 8 manuscripts between 2007 and 2012. Only 2 were seniored authored in journals with decent impact (Retrovirology and PLoS One). Prior to 2007, he published a review on TRIM proteins in Nat Rev Microbiol. In 2005 and first authored 4 research papers (PNAS in 2004; Exp Cell Res in 2002; JBC in 2002 and in 1999). The committee is concerned that if the publication record does not improve in the next period, the junior leader may lack the credentials to lead independently.

An other possible threat is represented by the fact that the research proposed is based on classic cellular biology and molecular biology techniques. These approaches may become obsolete or inadequate in the near future to maintain a high impact research project. An other possible threat is represented by the fact that this group has a small size, expecially when considered that it is led by 2 co-leaders.

 Recommendations:

The committee identified several areas that the team should address:

1. The publication record of the junior leader in recent years appears limited. He had a productive research record previously.Thus, it is likely that this deficiency represents the present status of development of ongoing projects. The committee expects that this deficiency is corrected by the time of the next review. The committee recommends that the senior leader and the unit leader provide mentoring in all aspects of career development. The junior leader should have the goal to develop an independent high profile research program that leads to senior authored publications in high impact journals. He should achieve national and international visibility. It is recommended that a career mentoring committee consisting of senior investigators is set up to review his progress by meeting at 6 months intervals. Mentoring commitees are used universally in the USA, Canada and Great Britain and are very usefull to foster the career of junior faculty. These efforts will be intrumental to promote a seamless transition in leadership for team 7 for upon the retirement of the senior leader in 5-6 years.

2. The group bases its research on classic molecular and cellular biology techniques. The committee reccomends the consideration of cutting edge research technologies such as genetically engineered mouse models to determine in vivo the relevance of their findings. The committee also suggests that the team should consider the use of RNAi or small compound libraries and biostatistical methods.

3. The team should increase its size by adding a full time research technician and additonal trainees (possibly international). Thus, the team should agressively seek additional funding including from European Union sources.

Team 8 : New Therapeutic Approaches of Myelination

Name of team leader: Mr Charbel MASSAAD

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	5 (2.5 ETP)	5 (2.5 ETP)	5 (2.5 ETP)
N2: Permanent EPST or EPIC researchers and similar positions	1	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	2	1
N6: Other contractual staff (without research duties)		2 (ANR contacts)	2 (ANR contacts)
TOTAL N1 to N6	8 (5.5 ETP)	11 (8.5 ETP)	9 (7.5 ETP)

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

This is a very strong team with an impressive team leader, who, in addition to running a research group with an upward trajectory, has a substantial administrative load as Dean of the Faculty of Biomedicine and a large teaching commitment. In a relatively short space of time the team leader has assembled a large and growing research group that is well-funded, productive and with a clear sense of direction. The team leader is relatively new to the myelin field so has yet to achieve the level of recognition and influence that his contributions merit. However, the committee believes that if he continues to be as productive as he has been then he will soon be acknowledged as one of the key players in the myelin regeneration field.

Assessment of scientific quality and outputs

This team is productive and has published several outstanding papers (with more to come based on the unpublished data that was presented). It includes 38 scientific articles published in international journals leading to more than 460 citations. There has been one *PNAS* paper, which describes one of the very few credible translational drug-based approaches to treating Charcot-Marie-Tooth Disease, a debilitating genetic demyelinating condition of the peripheral nervous system. This study, led by this team, involved collaboration with an internationally leading myelin research group in Germany who are known only to collaborative with outstanding labs on outstanding projects. This work attracted substantial media attention and is a 'major breakthrough in the field'. There has have also been two papers (again, led by this team) in the *Journal of Neuroscience*, one of the leading and most prestigious journals in the neurosciences, with a status and impact that exceeds its impact factor.

Assessment of the unit's academic reputation and appeal

The team leader is relatively new to the myelin field and has not yet established himself as one of its more prominent players. He has been invited to speak at several meetings but has not yet achieved the recognition that leads to invitations for keynote lectures at major international meetings. He has an attractively modest manner that contrasts with more pushy colleagues in the scientific community who proactively put themselves in the way of invitations to present at conferences and meetings. We are confident that more substantial invitations will come. In the meantime he has a growing international reputation as a careful and innovative scientist producing work of excellent quality. This is reflected in the increasing number of international collaborations that this team is assembling. The interactions that the team is establishing (or will establish) with clinical groups in and around Paris (e.g. Kremlin-Bicêtre - PNS, Salpêtrière - CNS) are very welcome and speak to a serious intention to translate the team laboratory studies into clinical advances.

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

As with the previous category, although the team and its leader are on an upward trajectory they have still to realise their full potential in this regard. Nevertheless, the team leader has had interactions with industry and the work of the team has been well and widely disseminated.

Assesment of the unit's organisation and life

This is a very harmonious team. The masters students and PhD students, who some Committee members made a point of talking to, spoke very highly of the way the group is managed. All the indications regarding team governance were very positive.

Assessment of the unit's involvement in training through research

As indicated, some Committee members made a point of talking to the masters and PhD students in this team. They have rarely encountered such an optimistic, engaged and focused group. This speaks volumes for the quality of the training environment. The evaluation team that spoke to the students and post-docs from the entire unit emphasized how vocal and engaged the members of this team were in particular. The team leader makes a very active attempt to get his students to interact, visit and engage with other scientists in the field – again, evidence of a first rate training environment.

Assessment of the five-year plan and strategy

Most aspects of the proposed programme are excellent and appropriately build on their recent impressive progress. The work on depression is high risk but there is sufficient evidence to make it well worth pursuing – and the potential rewards are very high indeed. The weakest part of the plan is the work on traumatic brain injury, which is too speculative and unlikely, in our view, to prove very fruitful.

Conclusion

 Strengths and opportunities:

- Strong leadership
- Important question with real potential translational benefits
- Good track record
- Clear sense of purpose and focus within the research group
- Good prospects for continued and increased funding
- Good prospects of strengthening industry links
- Strong position to strengthen national and international collaborations
- Excellent opportunities for interaction within other teams in the unit

 Weaknesses and threats:

- Some of the research topics are high risk (depression) or too speculative (Traumatic brain injury)

 Recommendations:

An excellent team that would benefit from joining the unit. The unit would undoubtedly benefit from incorporating this team. Unequivocal recommendation that this team be fully supported.

Team 9 : Neuromuscular degeneration and plasticity

Name of team leader: Mr Frédéric CHARBONNIER

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	7 (3.5)	7 (3.5)	7 (3.5)
N2: Permanent EPST or EPIC researchers and similar positions	1	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.)			
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	10	10	8

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

The various research projects are highly original and have led to several landmark studies in the relevant field. This is particularly obvious for the work dealing with mechanistically dissecting the beneficial impact of exercise training on the phenotype of neuromuscular disorders (i.e. amyotrophic lateral sclerosis, ALS and spinal muscular atrophy, SMA).The fact that the team is able to make fundamental advances and discoveries in this regard is very impressive, similar to the fact that 2 important neuromuscular disorders are being studied.Also, impressive is the variety of approaches used to monitor the impact of exercise on disease progression.This ranges from detailed molecular studies to highly significant physiological experimentation and clinical trials.In that context, the arrival of a new researcher with clear and demonstrated expertise in the cell and molecular biology of the protein SMN is highly regarded as it will nicely complement the work already on-going in this laboratory.

The work dealing with micro-RNAs and the role of calcineurin/NFATc2 signalling adds an important dimension to the team.Although much has been published by several other groups on the role of calcineurin and NFATc1 in muscle growth, a better understanding of additional factors is needed if the ultimate goal is to obtain a systematic and comprehensive view of all elements involved in controlling muscle fibre size and number.

During the 2007-2012 period, the team published 33 scientific articles in international journals leading to more than 369 citations. It includes publications in top-ranked Neuroscience and Physiology journals such as J Neuroscience (2008, 2010), J Cell Science (2012), J Physiol (2009, 2012).

Overall, the committee rates the novelty, quality of the work and productivity of the team as excellent with some clear outstanding contributions.Some of these contributions are pioneering studies with trend-setting implications and even practice-changing impact for patients.The fact that lab members are routinely and consistently publishing in top-ranked Neuroscience and Physiology journals represents strong evidence of the innovative and importance of their work, carried-out despite many of the researchers having important teaching and administrative responsibilities.

Assessment of the unit's academic reputation and appeal

This Team has undoubtedly acquired over the last several years, an enviable international reputation as a leading group in neuromuscular disorders and the use of exercise as a therapeutic intervention.This work has opened many new avenues for other groups interested in SMA and ALS around the world.As mentioned above, the work is very much seen as trend-setting with clear potential benefits for patient populations. Invitations to present at international meetings confirm this.Thus, because of the unique and innovative research program, impact of the work in the field and broad expertise of the Team, this Team is very attractive not only from a recruitment and retention perspective of trainees and researchers but also, for continued success with an internationally-competitive research program paralleled by further growth in excellence recognition.

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

The work led by this Team has led to 2 patents, the creation of a novel and much needed mouse exercise equipment for development by industry, and clinical implications with appropriate patient populations. This constitutes excellent impact within a relatively short period of time.These achievements, together with a remarkable teaching commitment to various programs, many leadership roles of key members of this Team and the obvious Academic recognition they receive, highlights the strong contributions and many varied unique interactions of Team members with several key groups of stakeholders.One should note however that on the front of social, economic, and cultural impact, the Team as a whole is clearly on an upward trend with more and greater concrete impact on various environments.It is expected to continue and even expand given the novelty and importance of their discoveries.

Assesment of the unit's organisation and life

The Team is very well organized into coherent subgroups and managed effectively despite having a varied composition made up of Profs, Teachers, Researchers and Trainees.In this context, the team leader exerts a clear positive influence, not only on the laboratory atmosphere but also in terms of guiding and coordinating effectively the work involved within the different sub-projects.As evidenced by his role as Vice-Dean, Member of Paris-Descartes Board and as the sought-after Director of a developing Federative Institute, the head of Team 9 has strong and demonstrated leadership skills.Yet, he is also capable of maintaining a collegial, supportive and collaborative management style.This is highly valued particularly in leading a front-line research group with many competitive research projects.The fact that the Team has grown in recent years and recruited new key personnel represents excellent and further evidence of the pleasant life and supportive environment within the Team.

Assessment of the unit's involvement in training through research

A number of PhD students and PDF are, or have been, associated with the Team. Many of these individuals have carried-out work that has led to first-authored publications in top journals. The Team provides Trainees with cutting-edge research projects and supports them with state-of-the-art, multidisciplinary methodological approaches. The Team appears also sufficiently funded to allow Trainees to travel to meetings when and where appropriate. In addition, many members of the Team are experienced investigators who provide mentoring to Trainees beyond simply guiding specific aspects of research projects and the intricacies linked to carrying-out laboratory work. This is critical in developing the next generation of scientists.Finally, Team members also participate significantly to Academic, research-oriented programs in terms of both teaching and administrative duties.

Assessment of the five-year plan and strategy

The five-year plan is exceedingly well prepared and carefully though-out to build upon the many recent and exciting findings obtained by Team members.The strategic plan is incorporated into 3 logically-organized work packages that allow interdisciplinarity and interactions amongst Team members.The plan includes several specific and highly innovative projects which will ensure that the Team remains a leading authority in this area gaining concomitantly further national and international recognition.The methodological approaches are diverse, complementary and highly appropriate.It iparticularly impressive to see how the different projects and subprojects are all integrated into a coherent experimental scheme and overall vision.I have no doubt that many additional key discoveries resulting in high impact publications will be obtained.

Conclusion

 Strengths and opportunities:

-An outstanding Team with many highly innovative and competitive research programs/projects.

-Team members have strong expertise in many key areas which will allow them to continue in this line of work in a timely and efficient fashion, resulting in additional high-impact publications

-Team leadership is definitely viewed as a strong asset to the Team, Faculty and University, helping in particular, Team 9 to work effectively and harmoniously.

-The combination of so many positive factors should provide the Team with significant opportunities for: 1) additional recruitment of highly-qualified personnel, top students and PDF; 2) substantial funding from various agencies; 3) growth of international collaborations; and 4) increased recognition. Additionally, Team members are ideally positioned to also make important contributions beyond the confined of their own laboratory particularly in teaching and developing broad-based initiatives.

 Weaknesses and threats:

There are no weaknesses identified within this Team.Although I am very impressed by the teaching commitments of many Team members and their involvement in significant administrative responsibilities and leadership roles, one has to be cautious that these activities, nonetheless, do not detract them from achieving their full potential as premier, internationally-recognized research Team.

 Recommendations:

Continue with the excellent work.

Remain aware that involvement in teaching and administration, although necessary and desirable, may negatively impact the overall progress of specific projects.

Recruitment of PDF would be desirable.In that sense, more Trainees from outside France would also be beneficial.However, through its ever-increasing recognition, the Team will be able to attract additional top students and PDF from elsewhere.

5 • Conduct of the visit

Visit dates:

Start:	January 16th, 2013, 8:30 AM
End:	January 17th, 2013, 6:30 PM

Visit site:	UMR-S 747 INSERM-Université Paris Descartes
Institution:	Université Paris Descartes
Address:	45, rue des Saints Pères, 75006 Paris

Specific premises visited:

Most of not all of the time available was dedicated for discussions and presentations. Nevertheless, some members of the commission laboratories found the time to visit some laboratories.

Conduct or programme of visit:

The visit was made according the following agenda:

- Conversation behind closed doors between members of the Committee to remember the rules of the evaluation made by the AERES scientific advisor;

- Research unit Director presentation (introduction, history, local and general context)

- Scientific presentation by the group leaders of the nine teams composing the research unit;

- Meeting with each category of personnel (engineers, technicians, administrative and technical staff, PhD students, post-docs);

- Research unit Director presentation (5 years plan and strategy)

- Discussion with the managing bodies

- Discussion behind closed doors between the Committee members.

Specific points to be mentioned:

- Mr Stefano MARULLO, Vice-President of the University Paris-Descartes, took part to the discussion with the representatives of managing bodies, and with Mr Frédéric DARDEL, President of the University Paris-Descartes and Mr Nicolas JEANJEAN, INSERM. They expressed their interest in the unit and their hope as to its role in the next structuration of the UFR Biomédicale des Saint Pères.

- Several observers, representatives of the managing bodies attended the presentations of the Director of the research unit and the team leaders during the two-days visit:

Ms Marie-Josèphe LEROY-ZAMIA, Chargée de Mission, Département de l'évaluation et du suivi des programmes à l'INSERM
Ms Catherine LABBE-JULLIE, Chargée de mission recherche, University Paris-Descartes

6 • Statistics by field: SVE on 10/06/2013

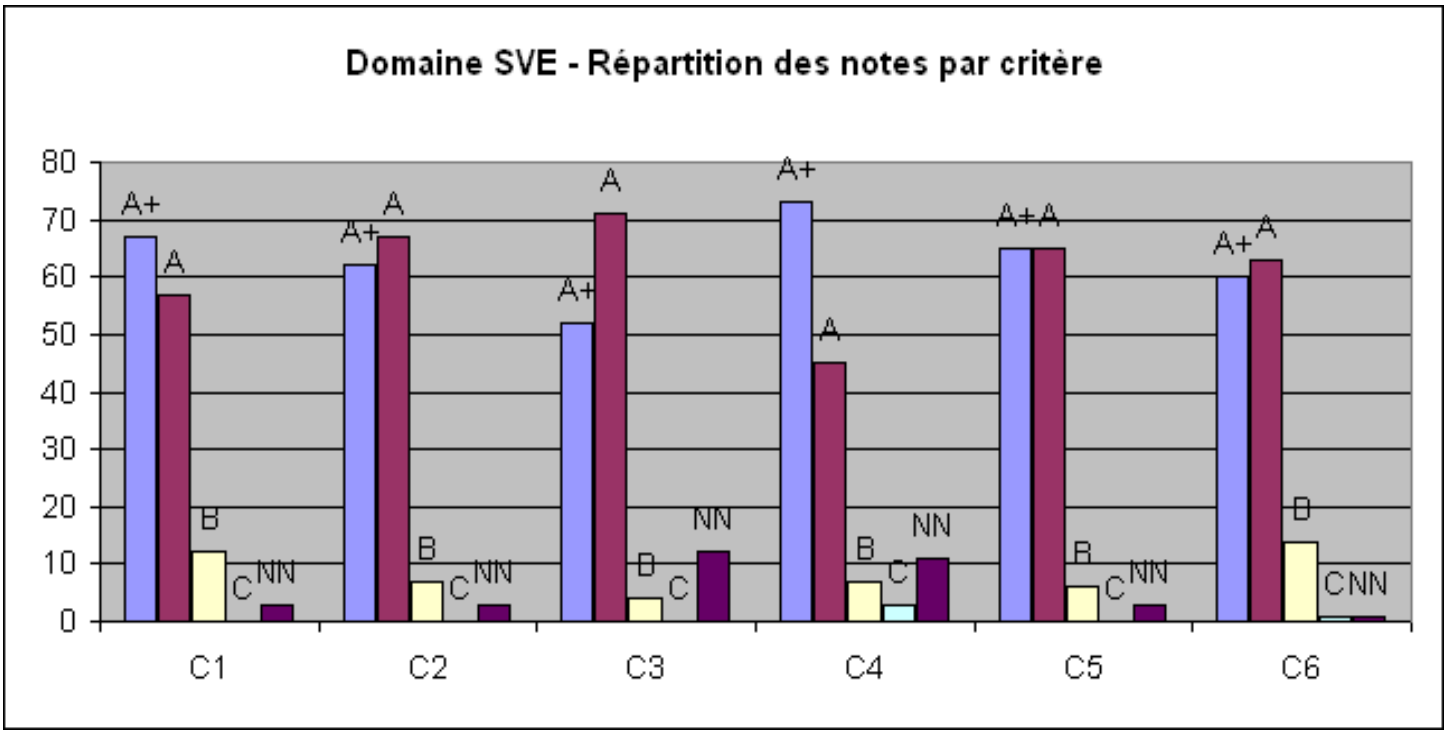
Grades

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	67	62	52	73	65	60
A	57	67	71	45	65	63
B	12	7	4	7	6	14
C	0	0	0	3	0	1
Non Noté	3	3	12	11	3	1

Percentages

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	48%	45%	37%	53%	47%	43%
A	41%	48%	51%	32%	47%	45%
B	9%	5%	3%	5%	4%	10%
C	0%	0%	0%	2%	0%	1%
Non Noté	2%	2%	9%	8%	2%	1%

Histogram



7 • Supervising bodies' general comments

UNIVERSITÉ PARIS DESCARTES

Vice Président du Conseil Scientifique

Paris le 02.04.2013

Vos ref : S2PUR140006461 –
Toxicologie Pharmacologie et
Signalisation Cellulaire - 0751721N

Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
Agence d'Evaluation de la Recherche et de
l'Enseignement Supérieur
20, rue Vivienne
75002 PARIS

Monsieur le Directeur

Je vous adresse mes remerciements pour la qualité du rapport d'évaluation fourni à l'issue de la visite du comité d'expertise concernant l'unité « Toxicologie Pharmacologie et Signalisation Cellulaire »

Vous trouverez ci-joint les réponses du Directeur de l'unité, Robert BAROUKI.

La volonté de l'Université est bien de soutenir l'effort de regroupement des équipes de toxicologie, pharmacologie chimie et biologie cellulaire pour fonder un centre pluridisciplinaire performant dans sa complémentarité.

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

Le Vice Président du Conseil Scientifique

Stefano Marullo, DM, DesSci

Université Paris Descartes, Vice-présidence du conseil scientifique, 12 rue de l'école de médecine, 75170 PARIS cedex 06
Téléphone: 01 76 53 17 45; Courriel: stefano.marullo@parisdescartes.fr

Reply to the AERES committee report on unit UMR-S 747 Inserm-Université Paris Descartes.

We would like to thank the committee for the professional manner in which the visit was conducted, for their detailed assessment of the unit and for their suggestions for improving the unit's project. As a whole, it is our opinion that the AERES committee report accurately assesses our unit's achievements and projects and we agree and take great pride in the committee's evaluation of our unit research as being excellent. Although the report mentions some weaknesses, many of these were already stated in our SWOT analysis for which we have proposed relevant actions. These points will not be discussed further here. The committee has made some recommendations, some of which support our general strategy, which will be very useful for us. We appreciate that. However, there are some specific statements in the report that require some clarification. These statements reflect discussions with the committee during the visit but, taken out of their context, they may be misleading to the reader. The comments below are provided, therefore, to help further clarify these issues.

Comments on the Unit

Strategy:

The statement on page 10 may be misleading: "It is the point of view of the evaluation committee that so far the strategy governing the unit expansion and evolution has largely been based on opportunistic recruitment of Teams ». This issue was discussed during the visit and focused on the team recruitment process in view of our long-term objectives.

As correctly stated in the assessment of the unit page 5, our long-term objective is to build a Department of molecular and cellular pharmacology and toxicology that is complementary to the chemistry unit and the other units of the federation. Therefore, we have been seeking to recruit teams with diverse and complementary expertise, mostly in cell signaling, and we have achieved that, as stated clearly (and praised) several times in the report, notably on page 5. It is also mentioned that diversity could be a threat but because of the excellent interactions between the teams, it is, in fact, an asset. We agree with the latter statement and we believe that it reflects the quality of our strategy and management.

Some of the committee members suggested that a good strategy would be to identify scientific needs and to launch international calls to recruit teams. This has been done in fact at the level of the federations and two independent units were recruited several years ago with the support of the university. It was not possible to repeat this at the unit level, therefore we used other mechanisms such as the Atipe-Avenir funds, or direct contacts with high quality teams having complementary expertise. This is how we were able to recruit teams in structural biology (team 4), stem cells (team 5) and in translational pharmacological research (team 3). All these themes are complementary to the initial unit themes and in line with our long-term objectives even if the teams were not recruited through international calls. In addition, these teams have produced high quality science which is reflected by their articles in *Science*, *Nature* and *NEJM*, for example.

Strategy also consists in having a local policy for increased cohesion within the federation. This has motivated the incorporation into the unit of teams 7, 8 and 9 for the next term. We have, therefore, acquired a real potential as a Department in the federation that is complementary to the chemistry unit. These new teams have been very well evaluated and the pharmacological implications of their projects were highlighted and praised by the committee in several sections of the report. We would like to cite one of the comments on team 8: "An excellent team that would benefit from joining the unit. The unit would undoubtedly benefit from incorporating this team ». This does seem like a good move and we believe that it is also a good strategic decision for the visibility and the future of the Center.

Concerning the strategic vision of the unit, the committee makes several suggestions :

- To recruit an additional team in chemical toxicology. This is exactly what we stated in our written document and oral presentation. We thank the committee for its support for our strategy. We do agree that this could be executed through an international call with the help of the university, INSERM and CNRS and the federation.
- To improve genome wide approaches and bioinformatics within the unit. Our approach is more in line with the university's approach which is to rely on shared technological platforms which are strongly supported by the university in this field. In addition, some scientists in our unit have developed expertise in these fields. We understand the suggestion of the committee but we believe that our approach is more realistic when considering the constraints of the French research system.
- To establish a scientific advisory board (SAB) and a mentoring system. In the case of the SAB, and as stated in our document, we plan to do that for the federation which will increase our interactions with the other units of the Center. As for mentoring, it is, in fact, done in practice although not being officially organized. We believe that this is a good suggestion and we plan to better structure this activity.

Other comments concerning EU funding and international networks will be discussed in the context of comments that concern each team. We currently have EU and NIH funding and we agree that this should be increased. We have taken steps in that regard and we participate actively in several European networks as will be discussed further later.

To conclude on these points, we believe that the report shows, in fact, that we had (and have) a successful and realistic strategy for the progressive expansion of the unit. The unit now constitutes what is effectively a strong department in the field of signaling, pharmacology and toxicology. That was our aim. Having a long-term strategy does not mean that we should not be capable of seizing opportunities to recruit teams. On the contrary, we believe that some degree of opportunism is a sign of dynamic management. We have a realistic approach that is compatible with the available funds and the French system. Whatever the means, we believe that the profile of our unit is now similar to that of equivalent successful departments elsewhere in the world.

Strategy for young leaders:

Another strategic vision of our project consists of an active support for young leaders. All of the future teams of the unit will have either a director, or a co-director, who will be under 50 years of age and who will have proven scientific and leadership capacities. More

specifically, this policy has resulted in a change of the director for team 1, new co-directors for teams 5 and 7 and the spin-off of a new team (team 6). The strategy underlying this last decision is discussed more extensively in the following paragraph.

We propose the constitution of team 6 as part of the unit strategy which is stated above. The constitution of the team is supported by several arguments. Team 6 has an ambitious and clearly identified project. The scientific quality of team 6 (as demonstrated by the publication records of the team's members) and the leadership of the team director (her participation in public health committees, her editorial functions, etc.) have been acknowledged by the committee. Regarding funding, the team leader recently obtained a grant from ARC and is associated with 3 ANR proposals this year. From this beginning, we are very confident about her ability to fund her research in the future. Further, the unit is committed to supporting, as necessary, her research until she obtains additional grants. The spin off of team 6 from team 5 is entirely in keeping with our policy to promote the autonomy of young investigators.

Comments on team 1

We agree with the general comments in the report concerning the importance and the relevance of the projects of the team for public health and with respect to the commitment of the team to perform very good science, teaching and dissemination of information to the public. We also note the support of the committee for the new team leader. We are grateful for these comments. There are, however, some points that need further elaboration.

- International recognition. There are some contradictions in the report on this aspect. On one hand, the report states that although the team has a very strong national recognition it has a less impressive international recognition. On the other hand, it provides objective evidence for the international visibility of the team. Here are some facts and figures: members of the team were invited to talk at ***19 of the most prestigious international meetings*** during the period under evaluation (Eurotox, IUTOX, PPTOX III sponsored by SOT, international meeting on inflammation, etc.). Members of the team played key roles in the organization of several international meetings including PPTOX; one team member will give a keynote lecture in the next International Congress of Toxicology in Seoul, July 2013. Concerning collaborative publications, it is easy to see that team 1 members co-publish with very prestigious scientists abroad, for example Pr. P. Fernandez-Salguero in Spain (AhR KO mice), or Dr. Linda Birnbaum, the NIEHS director. The team has received specific visits from several prominent scientists from around the world, for example Pr. B. Moorthy from MD Anderson, Pr. Bill Slikker, President of the SOT and head of the FDA National Centre for Toxicological Research, to name a few. In addition, the team has contributed to white papers that are highly relevant for public health together with the best scientists world-wide, the latest commentary in *the Lancet* on the epidemics of Non Communicable Diseases being an example. The future team leader is ***in charge of the organization of the Febs/EMBO meeting in 2014*** in Paris and he collaborates with several groups mentioned above. Based upon these facts, we believe that our team is **highly recognized on an international level** and is among the top French teams in the field in this respect.

- Concerning European funding and networks, we do agree (and we stated that) that, currently, the team does not have EU funding. However, the team is involved in several networks. In addition to close interactions with Pr. Frernandez-Salguerro (Spain), the institute of Environmental Sciences in Dusseldorf, several laboratories in Brno and Olomouc (Czech Republic), ***the team is part of a European network*** (Eureka) that submitted an EU proposal last year on exposome research. Although selected in the first round, the proposal did not obtain funding in the final round. With the same network (more than 20 laboratories from all over Europe), the team is participating in the Heals proposal this year. This proposal has passed the first round of the selection procedure and notification concerning funding in the final round is pending.
- As stated by the reviewer, the team does have a very good national recognition and a very large number of invitations to conferences. This is due, in part, to the efforts to interact with other fields. For example, 4 members of the team, including the team leader, contribute regularly to nutrition and obesity meetings. Team members are also invited to meetings in gynecology and cancer.
- Concerning the number of students per HDR. Although this number was found to be relatively low by the reviewer, it is related to our strict policy concerning student supervision. First, some of the Professors or assistant professors in the unit, with HDRs, are clinicians and have heavy clinical duties. Their contribution is important for our translational work. However, it would be unwise for them to supervise PhD students on a daily basis. Therefore, the director of the team allows a student to be recruited only when the right management conditions are ensured. Another trivial explanation is that obtaining funding for more than one PhD student at the same time in the same Doctoral school in our French system is impossible (Doctoral school policy). We will keep our rigorous policy for student recruitment.
- Concerning publications. The team publishes in the best journals of its field (environment-health and toxicology) as well as in less specialized journals. In addition, the team leader has publications in very prestigious journals.
- There has been a comment on the number of projects. We would like to state that **all of our projects are funded by** one or several **external agencies** (ANR, ANSES, PNRPE, ARC, ITMO Cancer, etc.). We are certain that the committee can appreciate this success in project funding during a period in which research funding is scarce.

Comments on team 2

We are grateful for the comments of the AERES committee. As stated by the committee, we need to prioritize our projects in order to match human resources and project requirements and feasibility. Along these lines, and as previously stated, we will focus on the relaxin, soliotic and neutrophil projects. For the new members, our goal is to focus on the interaction between mechanical stress and oxidative stress. This has been extensively discussed with Dr Didier Borderie and we all agree on that. In addition, we just received a new grant allowing us to buy a new flexercell system in order to study 2D and 3D mechanical stress effects. This new equipment will allow us to perform the mechanical stress project under very good conditions. Lastly, concerning the drug development project, we have a contract with LFB in order to test their products in vivo. This was not presented in detail because of a confidentiality agreement between us and our industrial partner.

Comments on team 3

We warmly thank the committee and we have no additional comments.

Comments on team 4

We sincerely appreciate the general and positive comments from the committee with respect to our team. As already discussed during the visit, we agree with the comments on production of articles and will concentrate our efforts on publishing the scientific data already at hand. This will result in the HDR defense of the team leader in the coming months. In addition, to strengthen the team and move forward the projects, particularly the AhR project and the protein production/crystallization platform, an **Inserm engineer with a permanent position** will officially join us as of June 1st 2013. Thus, the team will consist of 3 members with permanent positions, an assistant (ATER) and a post doctoral fellow.

Comments on team 5

First of all, Team 5 thanks the committee for its general appreciation of our research activities.

We just want to comment about some threats pinpointed by the committee. In particular recommendation is made « to use more than one cell line in the work and verify data more extensively with primary cells and in vivo models ». It is true that our work mainly exploits the properties of the 1C11 neuroectodermal cell line which has the unique capacity to acquire upon induction (frequency almost 100%), the overall functional properties of either serotonergic ($1C11^{5\text{-}HT}$) or noradrenergic ($1C11^{NE}$) neurons, i.e. bioamine synthesis, storage and transport. As in *in vivo* conditions, the implementation of neuronal functions is controlled by external serotonin (5-HT) or norepinephrine (NE), via a set of autoreceptors selectively induced along either differentiation pathway. Notably, the dynamics of differentiation of this neuronal progenitor has allowed major scientific advances in the field of neurological diseases (prion, Alzheimer, depression). For instance, this cell line was seminal to assign a signaling function to the cellular prion protein (Science 2000, PNAS 2003, FASEB J 2012…) and to reveal the mode of action of Prozac via a microRNA (miR-16) (Science 2010, Trans Psy. 2011). Our current work with prion-infected 1C11 cells unravels TACE regulation through PrP^{C}-dependent control of PDK1 and posits PDK1 as a potential therapeutic target not only to alleviate prion disorders but also Alzheimer's disease (AD) (in revision). **As mentioned in the written AERES document and our oral presentation, the molecular and cellular mechanisms identified with the help of the 1C11 cell line were all confirmed with primary cultures (cerebellar granule neurons; adult hippocampal neurons from AD mice), animal models (mouse models of depression, prion-infected mice, PrP KO mice, mouse models of Alzheimer's disease) and patient samples (CSF of patients treated with Prozac and brain samples of AD patients).**

The committee finds « the work related to the tooth stem cells/progenitors not logically incorporated in the overall project/research line of the group ». We have established clonal cell lines from dental pulp cultures of mouse embryo (ED18) first molar and shown that multipotent cells are present within the pulp. Implantation of these stem cells in mouse incisor or rat molar promote efficient tooth repair after pulp injury.

Characterizing pulpal stem cell intrinsic functions and their ability to respond to external signals represents an ongoing challenge for tooth repair and regeneration. Of note, pulpal stem cells derived from the neural crest. As mentioned in the AERES project, we observed, using biochemical and pharmacological tools, that **our pulpal stem cell lines display features of bioaminergic cells** (unpublished data). This property is reminiscent of that of the 1C11 cell line, which acquires the overall functional properties of either serotonergic ($1C11^{5\text{-}HT}$) or noradrenergic ($1C11^{NE}$) neurons. Interestingly, our pulpal clones exhibit both serotonergic (5-HT) and dopaminergic (DA) metabolisms and display 5-HT and DA autoreceptors. Presumably, these receptors make pulpal stem cells competent to respond to 5-HT or DA. We are currently characterizing the role of these receptors in dental homeostasis and repair.
Minor point: The paper by Baudry et al on « $5\text{-}HT_{2B}$ receptor role in bone mineralization via TNAP » is not submitted as mentioned by the committee, but was published in 2010 in JBC.

Comments on team 6

We thank the committee for his careful assessment of our projects.

Regarding the interaction with the social, economic and cultural environment, the committee omitted to mention that the team leader is an expert in the French Committee on Transmissible Spongiform Encephalopathies (ANSES, French Food Safety Agency) since 2004.

Regarding the involvement in training through research, the team leader is currently supervising two PhD students. The team also includes one postdoctoral fellow, who is supported by a grant obtained by the team leader.

Regarding the weaknesses and recommendations:

1. It is claimed that the team has not secured additional funding.

The team has recently obtained a grant from ARC (2013-2014) and applied in early 2013 to ANR for funding. Three applications including one as coordinator are currently under evaluation. Further, the incorporation of new teams working in neurobiology within the unit will tighten already existing collaborations and increase prospects for future joint grant applications.

2. It is claimed that the team has no track record in the field of cancer stem cells and that it should concentrate on other projects prior to extending research towards new topics.

It is true that the "prion and cancer stem cell" project has been launched recently. The preliminary data obtained within the team support the feasibility of the project and reinforce the strategy to develop this topic. This project has received financial support (ARC contract 2013-2014), and thereby has been positively evaluated in terms of funding.

3. It is recommended to use other cell lines beyond the 1C11 cell line as well as primary cells and it is claimed that the 1C11 cell line might not be the optimal system for PrP related work. It is also recommended to more extensively validate data using in vivo models.

As recommended by the committee, the team's strategy is to exploit the 1C11 cell line and other cellular models to delineate pathophysiological processes and to validate the data obtained through in vivo analyses. This strategy proved to be successful in the past.

Along the microRNA axis, the 1C11 cell line has been instrumental in identifying miR-16 as a microRNA targeting the serotonin transporter and that of signalling molecules involved in the regulation of miR-16 (Baudry et al., Science 2010, Launay, Mouillet-Richard et al., Trans. Psy. 2011). These two studies exploited in vivo models to validate data obtained with 1C11 cells. The relevance of some data was also substantiated in patients (Trans. Psy. 2011).

The 1C11 cell line has also been instrumental in assigning a signalling function to the cellular prion protein (Mouillet-Richard et al, Science 2000), and further uncovering signal transduction cascades dependent on PrP^C, highlight a role for PrP^C in neuritogenesis, as well as to uncover molecular alterations induced by pathogenic prions (JBC 2008, Cell Death Dis. 2013). In some instances, data obtained with the 1C11 cell line have been recapitulated in primary cells e.g. GT1 cells (PNAS 2003), PC12 cells (FASEB J, 2012), neural stem cells (Cell Death Dis. 2013), cerebellar granule cells or even in vivo (Cell Death Dis. 2013, Nature Med in revision). Concerning the " prion and cancer stem cell" project, it exploits prostate cancer cells lines (LNCaP, PC3) and will include analyses on patient biopsies (collaboration JM Launay, Lariboisière Hospital, Paris).

4. The Committee suggests that the team should be involved in more international and national collaborations in order to increase publication record

Some collaborations that started a few years ago and have been successful. For instance, work with Stéphane Haik (CRIM, Pitié-Salpétrière Hospital, Paris) and Juan-Maria Torres (CISA, Madrid, Spain) started in mid 2009 and gave rise to a paper published in Cell Death and Disease last January.

Two other collaborations were launched in 2012 (KP Lesch, Wurzburg University, Germany; P Svenningsson, Karolinska Institute, Sweden) and are expected to yield common publications in the near future.

Nevertheless, as recommended, the team also intends to develop its network of collaborations in the near future.

Comments on team 7

The general scientific comments on Team 7 are very positive and nicely summarize the international input of the team in the field. We thank the committee for that. A few comments and clarifications are in order, however.

1- In “Assessment of scientific quality and outputs”

“The publications are mostly published as **first authors** in the best journals”. **Please note that the team members also appear as last authors on the publications.**

2- In **”**Assessment of the unit's involvement in training through research”

“Degrees awarded since 2007: 3 Ph.D theses, 1 engineering degree, 2 masters I and 3 masters II.” **Note that 2 Ph.D theses supervised by the junior scientist are missing.**

3- In “Weaknesses and threats”

“Another possible threat is represented by the fact that the research proposed is based on classic cellular biology and molecular biology techniques. These approaches may become obsolete or inadequate in the near future to maintain a high impact research project.” In fact our strategies are more diverse than this sentence may imply. This is actually clearly stated in the report**:** “In conclusion this is a team that has achieved a very good output both in terms of discoveries and in terms of publication record. More importantly, the applicability of the research performed is outstanding as demonstrated by the ongoing clinical trial. Moreover, the team’s novel method to identify SUMOylated proteins has gained general acceptance and is being used by several laboratories around the world.”

4- Comments concerning the junior leader

Many positive aspects have not been mentioned in this report concerning the junior leader.

-Since 2007, he obtained three grants (Sidaction 2007, ANRS 2007-08, ANRS 2013-15) as well as financial support for a post-doctoral fellow (2013-2015). Also, 2 Ph.D theses were defended under his direction.
- He already is recognized nationally and internationally as a specialist in his field, as illustrated by his activity as a member of the ANRS scientific committee (since 2009) and his evaluations for the Medical Research Council (UK, 2008), INSERM (2010), the Paris Diderot University (2006-2009) and several international journals (Journal of Biological Chemistry, Nature Reviews Immunology, FEBS Journal, Retrovirology, Leukemia Research, ...). Thus, it is as a recognized and productive scientist that the junior researcher has joined the team bringing with him his expertise on TRIM proteins and antiviral innate immunity. The complementarities of the projects are obvious and we strongly believe in the synergy of our expertise and competences.
-It is indicated in the report that "the junior leader has a "limited productivity as a senior author during the period under consideration". Reduced productivity was an inevitable compromise resulting from the evolution in the junior leader's career over the period of evaluation. Indeed, whereas he was a university lecturer initially, the junior leader obtained a position as a full-time INSERM scientist in 2010 and had to move to a different lab to fulfill his new temporary assignment. Given the complementarities of our projects, he decided to join our team in 2012. These two consecutive moves finally allowed us to build the team as it is now, but they also account for his "limited productivity" over the last two years.
The junior leader now has the opportunity finally to settle down and to develop "an independent high profile research program", as mentioned in the report. In 2012, he obtained additional financial support for 2013-2015 from ANRS, as well as a two-year postdoctoral grant. His recruitment, as a team co-leader, is already very fruitful for him as well as for the rest of the team. Indeed, he joined the team less than a year ago and 2 papers already have been submitted jointly. On one paper, the junior leader is the penultimate and corresponding author and on the other he is the first author. Another paper is in preparation and there is no doubt that our scientific production will be even more synergistic with time.
- As suggested in the AERES report, since the senior leader will stay for another 6 years, she will provide the junior leader with "mentoring in all aspects of career development". We fully agree with this recommendation, as we also believe this will allow a "seamless transition in leadership upon the retirement of the senior leader in 5-6 years".

Comments on team 8

We are grateful for the very positive comments of the committee. We agree that the research topics on depression and traumatic brain injury may be at high risk. Nevertheless, these two projects merit to be pursued because of their relevance for public health and because of the understanding of the role of myelin in depression and in injuries that they might provide. They are currently funded by the ANR, European Research Network (ERA-NET Neuron) and a private foundation (Les Gueules Cassées). For the next five years, we have proposed risky projects (and probably having a high reward) as well as more conventional ones.

Comments on team 9

We wish to thank the AERES committee for their very positive and encouraging comments. We fully appreciate the committee's comments on the time-consuming teaching and administrative duties of some team members. In fact, our team has made significant adjustments regarding these types of commitments with, in particular, a substantial reduction in teaching duties for the young researchers of the team. The administrative duties, mainly undertaken by senior team members, are also compensated for by a reduction in the statutory teaching duties.

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- To improve genome wide approaches and bioinformatics within the unit. Our approach is more in line with the university's approach which is to rely on shared technological platforms which are strongly supported by the university in this field. In addition, some scientists in our unit have developed expertise in these fields. We understand the suggestion of the committee but we believe that our approach is more realistic when considering the constraints of the French research system.
- To establish a scientific advisory board (SAB) and a mentoring system. In the case of the SAB, and as stated in our document, we plan to do that for the federation which will increase our interactions with the other units of the Center. As for mentoring, it is, in fact, done in practice although not being officially organized. We believe that this is a good suggestion and we plan to better structure this activity.

Other comments concerning EU funding and international networks will be discussed in the context of comments that concern each team. We currently have EU and NIH funding and we agree that this should be increased. We have taken steps in that regard and we participate actively in several European networks as will be discussed further later.

To conclude on these points, we believe that the report shows, in fact, that we had (and have) a successful and realistic strategy for the progressive expansion of the unit. The unit now constitutes what is effectively a strong department in the field of signaling, pharmacology and toxicology. That was our aim. Having a long-term strategy does not mean that we should not be capable of seizing opportunities to recruit teams. On the contrary, we believe that some degree of opportunism is a sign of dynamic management. We have a realistic approach that is compatible with the available funds and the French system. Whatever the means, we believe that the profile of our unit is now similar to that of equivalent successful departments elsewhere in the world.

Strategy for young leaders:

Another strategic vision of our project consists of an active support for young leaders. All of the future teams of the unit will have either a director, or a co-director, who will be under 50 years of age and who will have proven scientific and leadership capacities. More

specifically, this policy has resulted in a change of the director for team 1, new co-directors for teams 5 and 7 and the spin-off of a new team (team 6). The strategy underlying this last decision is discussed more extensively in the following paragraph.

We propose the constitution of team 6 as part of the unit strategy which is stated above. The constitution of the team is supported by several arguments. Team 6 has an ambitious and clearly identified project. The scientific quality of team 6 (as demonstrated by the publication records of the team's members) and the leadership of the team director (her participation in public health committees, her editorial functions, etc.) have been acknowledged by the committee. Regarding funding, the team leader recently obtained a grant from ARC and is associated with 3 ANR proposals this year. From this beginning, we are very confident about her ability to fund her research in the future. Further, the unit is committed to supporting, as necessary, her research until she obtains additional grants. The spin off of team 6 from team 5 is entirely in keeping with our policy to promote the autonomy of young investigators.

Comments on team 1

We agree with the general comments in the report concerning the importance and the relevance of the projects of the team for public health and with respect to the commitment of the team to perform very good science, teaching and dissemination of information to the public. We also note the support of the committee for the new team leader. We are grateful for these comments. There are, however, some points that need further elaboration.

- International recognition. There are some contradictions in the report on this aspect. On one hand, the report states that although the team has a very strong national recognition it has a less impressive international recognition. On the other hand, it provides objective evidence for the international visibility of the team. Here are some facts and figures: members of the team were invited to talk at ***19 of the most prestigious international meetings*** during the period under evaluation (Eurotox, IUTOX, PPTOX III sponsored by SOT, international meeting on inflammation, etc.). Members of the team played key roles in the organization of several international meetings including PPTOX; one team member will give a keynote lecture in the next International Congress of Toxicology in Seoul, July 2013. Concerning collaborative publications, it is easy to see that team 1 members co-publish with very prestigious scientists abroad, for example Pr. P. Fernandez-Salguero in Spain (AhR KO mice), or Dr. Linda Birnbaum, the NIEHS director. The team has received specific visits from several prominent scientists from around the world, for example Pr. B. Moorthy from MD Anderson, Pr. Bill Slikker, President of the SOT and head of the FDA National Centre for Toxicological Research, to name a few. In addition, the team has contributed to white papers that are highly relevant for public health together with the best scientists world-wide, the latest commentary in *the Lancet* on the epidemics of Non Communicable Diseases being an example. The future team leader is ***in charge of the organization of the Febs/EMBO meeting in 2014*** in Paris and he collaborates with several groups mentioned above. Based upon these facts, we believe that our team is **highly recognized on an international level** and is among the top French teams in the field in this respect.

- Concerning European funding and networks, we do agree (and we stated that) that, currently, the team does not have EU funding. However, the team is involved in several networks. In addition to close interactions with Pr. Frernandez-Salguerro (Spain), the institute of Environmental Sciences in Dusseldorf, several laboratories in Brno and Olomouc (Czech Republic), ***the team is part of a European network*** (Eureka) that submitted an EU proposal last year on exposome research. Although selected in the first round, the proposal did not obtain funding in the final round. With the same network (more than 20 laboratories from all over Europe), the team is participating in the Heals proposal this year. This proposal has passed the first round of the selection procedure and notification concerning funding in the final round is pending.
- As stated by the reviewer, the team does have a very good national recognition and a very large number of invitations to conferences. This is due, in part, to the efforts to interact with other fields. For example, 4 members of the team, including the team leader, contribute regularly to nutrition and obesity meetings. Team members are also invited to meetings in gynecology and cancer.
- Concerning the number of students per HDR. Although this number was found to be relatively low by the reviewer, it is related to our strict policy concerning student supervision. First, some of the Professors or assistant professors in the unit, with HDRs, are clinicians and have heavy clinical duties. Their contribution is important for our translational work. However, it would be unwise for them to supervise PhD students on a daily basis. Therefore, the director of the team allows a student to be recruited only when the right management conditions are ensured. Another trivial explanation is that obtaining funding for more than one PhD student at the same time in the same Doctoral school in our French system is impossible (Doctoral school policy). We will keep our rigorous policy for student recruitment.
- Concerning publications. The team publishes in the best journals of its field (environment-health and toxicology) as well as in less specialized journals. In addition, the team leader has publications in very prestigious journals.
- There has been a comment on the number of projects. We would like to state that **all of our projects are funded by** one or several **external agencies** (ANR, ANSES, PNRPE, ARC, ITMO Cancer, etc.). We are certain that the committee can appreciate this success in project funding during a period in which research funding is scarce.

Comments on team 2

We are grateful for the comments of the AERES committee. As stated by the committee, we need to prioritize our projects in order to match human resources and project requirements and feasibility. Along these lines, and as previously stated, we will focus on the relaxin, soliotic and neutrophil projects. For the new members, our goal is to focus on the interaction between mechanical stress and oxidative stress. This has been extensively discussed with Dr Didier Borderie and we all agree on that. In addition, we just received a new grant allowing us to buy a new flexercell system in order to study 2D and 3D mechanical stress effects. This new equipment will allow us to perform the mechanical stress project under very good conditions. Lastly, concerning the drug development project, we have a contract with LFB in order to test their products in vivo. This was not presented in detail because of a confidentiality agreement between us and our industrial partner.

Comments on team 3

We warmly thank the committee and we have no additional comments.

Comments on team 4

We sincerely appreciate the general and positive comments from the committee with respect to our team. As already discussed during the visit, we agree with the comments on production of articles and will concentrate our efforts on publishing the scientific data already at hand. This will result in the HDR defense of the team leader in the coming months. In addition, to strengthen the team and move forward the projects, particularly the AhR project and the protein production/crystallization platform, an **Inserm engineer with a permanent position** will officially join us as of June 1st 2013. Thus, the team will consist of 3 members with permanent positions, an assistant (ATER) and a post doctoral fellow.

Comments on team 5

First of all, Team 5 thanks the committee for its general appreciation of our research activities.

We just want to comment about some threats pinpointed by the committee. In particular recommendation is made « to use more than one cell line in the work and verify data more extensively with primary cells and in vivo models ». It is true that our work mainly exploits the properties of the 1C11 neuroectodermal cell line which has the unique capacity to acquire upon induction (frequency almost 100%), the overall functional properties of either serotonergic ($1C11^{5\text{-}HT}$) or noradrenergic ($1C11^{NE}$) neurons, i.e. bioamine synthesis, storage and transport. As in *in vivo* conditions, the implementation of neuronal functions is controlled by external serotonin (5-HT) or norepinephrine (NE), via a set of autoreceptors selectively induced along either differentiation pathway. Notably, the dynamics of differentiation of this neuronal progenitor has allowed major scientific advances in the field of neurological diseases (prion, Alzheimer, depression). For instance, this cell line was seminal to assign a signaling function to the cellular prion protein (Science 2000, PNAS 2003, FASEB J 2012…) and to reveal the mode of action of Prozac via a microRNA (miR-16) (Science 2010, Trans Psy. 2011). Our current work with prion-infected 1C11 cells unravels TACE regulation through PrP^{C}-dependent control of PDK1 and posits PDK1 as a potential therapeutic target not only to alleviate prion disorders but also Alzheimer's disease (AD) (in revision). **As mentioned in the written AERES document and our oral presentation, the molecular and cellular mechanisms identified with the help of the 1C11 cell line were all confirmed with primary cultures (cerebellar granule neurons; adult hippocampal neurons from AD mice), animal models (mouse models of depression, prion-infected mice, PrP KO mice, mouse models of Alzheimer's disease) and patient samples (CSF of patients treated with Prozac and brain samples of AD patients).**

The committee finds « the work related to the tooth stem cells/progenitors not logically incorporated in the overall project/research line of the group ». We have established clonal cell lines from dental pulp cultures of mouse embryo (ED18) first molar and shown that multipotent cells are present within the pulp. Implantation of these stem cells in mouse incisor or rat molar promote efficient tooth repair after pulp injury.

Characterizing pulpal stem cell intrinsic functions and their ability to respond to external signals represents an ongoing challenge for tooth repair and regeneration. Of note, pulpal stem cells derived from the neural crest. As mentioned in the AERES project, we observed, using biochemical and pharmacological tools, that **our pulpal stem cell lines display features of bioaminergic cells** (unpublished data). This property is reminiscent of that of the 1C11 cell line, which acquires the overall functional properties of either serotonergic ($1C11^{5\text{-}HT}$) or noradrenergic ($1C11^{NE}$) neurons. Interestingly, our pulpal clones exhibit both serotonergic (5-HT) and dopaminergic (DA) metabolisms and display 5-HT and DA autoreceptors. Presumably, these receptors make pulpal stem cells competent to respond to 5-HT or DA. We are currently characterizing the role of these receptors in dental homeostasis and repair.
Minor point: The paper by Baudry et al on « $5\text{-}HT_{2B}$ receptor role in bone mineralization via TNAP » is not submitted as mentioned by the committee, but was published in 2010 in JBC.

Comments on team 6

We thank the committee for his careful assessment of our projects.

Regarding the interaction with the social, economic and cultural environment, the committee omitted to mention that the team leader is an expert in the French Committee on Transmissible Spongiform Encephalopathies (ANSES, French Food Safety Agency) since 2004.

Regarding the involvement in training through research, the team leader is currently supervising two PhD students. The team also includes one postdoctoral fellow, who is supported by a grant obtained by the team leader.

Regarding the weaknesses and recommendations:

1. It is claimed that the team has not secured additional funding.

The team has recently obtained a grant from ARC (2013-2014) and applied in early 2013 to ANR for funding. Three applications including one as coordinator are currently under evaluation. Further, the incorporation of new teams working in neurobiology within the unit will tighten already existing collaborations and increase prospects for future joint grant applications.

2. It is claimed that the team has no track record in the field of cancer stem cells and that it should concentrate on other projects prior to extending research towards new topics.

It is true that the "prion and cancer stem cell" project has been launched recently. The preliminary data obtained within the team support the feasibility of the project and reinforce the strategy to develop this topic. This project has received financial support (ARC contract 2013-2014), and thereby has been positively evaluated in terms of funding.

3. It is recommended to use other cell lines beyond the 1C11 cell line as well as primary cells and it is claimed that the 1C11 cell line might not be the optimal system for PrP related work. It is also recommended to more extensively validate data using in vivo models.

As recommended by the committee, the team's strategy is to exploit the 1C11 cell line and other cellular models to delineate pathophysiological processes and to validate the data obtained through in vivo analyses. This strategy proved to be successful in the past.

Along the microRNA axis, the 1C11 cell line has been instrumental in identifying miR-16 as a microRNA targeting the serotonin transporter and that of signalling molecules involved in the regulation of miR-16 (Baudry et al., Science 2010, Launay, Mouillet-Richard et al., Trans. Psy. 2011). These two studies exploited in vivo models to validate data obtained with 1C11 cells. The relevance of some data was also substantiated in patients (Trans. Psy. 2011).

The 1C11 cell line has also been instrumental in assigning a signalling function to the cellular prion protein (Mouillet-Richard et al, Science 2000), and further uncovering signal transduction cascades dependent on PrP^C, highlight a role for PrP^C in neuritogenesis, as well as to uncover molecular alterations induced by pathogenic prions (JBC 2008, Cell Death Dis. 2013). In some instances, data obtained with the 1C11 cell line have been recapitulated in primary cells e.g. GT1 cells (PNAS 2003), PC12 cells (FASEB J, 2012), neural stem cells (Cell Death Dis. 2013), cerebellar granule cells or even in vivo (Cell Death Dis. 2013, Nature Med in revision). Concerning the " prion and cancer stem cell" project, it exploits prostate cancer cells lines (LNCaP, PC3) and will include analyses on patient biopsies (collaboration JM Launay, Lariboisière Hospital, Paris).

4. The Committee suggests that the team should be involved in more international and national collaborations in order to increase publication record

Some collaborations that started a few years ago and have been successful. For instance, work with Stéphane Haik (CRIM, Pitié-Salpétrière Hospital, Paris) and Juan-Maria Torres (CISA, Madrid, Spain) started in mid 2009 and gave rise to a paper published in Cell Death and Disease last January.

Two other collaborations were launched in 2012 (KP Lesch, Wurzburg University, Germany; P Svenningsson, Karolinska Institute, Sweden) and are expected to yield common publications in the near future.

Nevertheless, as recommended, the team also intends to develop its network of collaborations in the near future.

Comments on team 7

The general scientific comments on Team 7 are very positive and nicely summarize the international input of the team in the field. We thank the committee for that. A few comments and clarifications are in order, however.

1- In “Assessment of scientific quality and outputs”

“The publications are mostly published as **first authors** in the best journals”. **Please note that the team members also appear as last authors on the publications.**

2- In **”**Assessment of the unit's involvement in training through research”

“Degrees awarded since 2007: 3 Ph.D theses, 1 engineering degree, 2 masters I and 3 masters II.” **Note that 2 Ph.D theses supervised by the junior scientist are missing.**

3- In “Weaknesses and threats”

“Another possible threat is represented by the fact that the research proposed is based on classic cellular biology and molecular biology techniques. These approaches may become obsolete or inadequate in the near future to maintain a high impact research project.” In fact our strategies are more diverse than this sentence may imply. This is actually clearly stated in the report**:** “In conclusion this is a team that has achieved a very good output both in terms of discoveries and in terms of publication record. More importantly, the applicability of the research performed is outstanding as demonstrated by the ongoing clinical trial. Moreover, the team’s novel method to identify SUMOylated proteins has gained general acceptance and is being used by several laboratories around the world.”

4- Comments concerning the junior leader

Many positive aspects have not been mentioned in this report concerning the junior leader.

-Since 2007, he obtained three grants (Sidaction 2007, ANRS 2007-08, ANRS 2013-15) as well as financial support for a post-doctoral fellow (2013-2015). Also, 2 Ph.D theses were defended under his direction.
- He already is recognized nationally and internationally as a specialist in his field, as illustrated by his activity as a member of the ANRS scientific committee (since 2009) and his evaluations for the Medical Research Council (UK, 2008), INSERM (2010), the Paris Diderot University (2006-2009) and several international journals (Journal of Biological Chemistry, Nature Reviews Immunology, FEBS Journal, Retrovirology, Leukemia Research, ...). Thus, it is as a recognized and productive scientist that the junior researcher has joined the team bringing with him his expertise on TRIM proteins and antiviral innate immunity. The complementarities of the projects are obvious and we strongly believe in the synergy of our expertise and competences.
-It is indicated in the report that "the junior leader has a "limited productivity as a senior author during the period under consideration". Reduced productivity was an inevitable compromise resulting from the evolution in the junior leader's career over the period of evaluation. Indeed, whereas he was a university lecturer initially, the junior leader obtained a position as a full-time INSERM scientist in 2010 and had to move to a different lab to fulfill his new temporary assignment. Given the complementarities of our projects, he decided to join our team in 2012. These two consecutive moves finally allowed us to build the team as it is now, but they also account for his "limited productivity" over the last two years.
The junior leader now has the opportunity finally to settle down and to develop "an independent high profile research program", as mentioned in the report. In 2012, he obtained additional financial support for 2013-2015 from ANRS, as well as a two-year postdoctoral grant. His recruitment, as a team co-leader, is already very fruitful for him as well as for the rest of the team. Indeed, he joined the team less than a year ago and 2 papers already have been submitted jointly. On one paper, the junior leader is the penultimate and corresponding author and on the other he is the first author. Another paper is in preparation and there is no doubt that our scientific production will be even more synergistic with time.
- As suggested in the AERES report, since the senior leader will stay for another 6 years, she will provide the junior leader with "mentoring in all aspects of career development". We fully agree with this recommendation, as we also believe this will allow a "seamless transition in leadership upon the retirement of the senior leader in 5-6 years".

Comments on team 8

We are grateful for the very positive comments of the committee. We agree that the research topics on depression and traumatic brain injury may be at high risk. Nevertheless, these two projects merit to be pursued because of their relevance for public health and because of the understanding of the role of myelin in depression and in injuries that they might provide. They are currently funded by the ANR, European Research Network (ERA-NET Neuron) and a private foundation (Les Gueules Cassées). For the next five years, we have proposed risky projects (and probably having a high reward) as well as more conventional ones.

Comments on team 9

We wish to thank the AERES committee for their very positive and encouraging comments. We fully appreciate the committee's comments on the time-consuming teaching and administrative duties of some team members. In fact, our team has made significant adjustments regarding these types of commitments with, in particular, a substantial reduction in teaching duties for the young researchers of the team. The administrative duties, mainly undertaken by senior team members, are also compensated for by a reduction in the statutory teaching duties.