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

Department for the evaluation of research units

AERES report on unit:

Promoting Research Oriented Toward Early Cns Therapy

PROTECT

Under the supervision of the following institutions and research bodies:

Université Paris 7 – Denis Diderot

Institut national de la santé et de la recherche médicale

Centre National de la Recherche Scientifique

January 2013

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

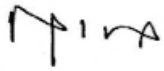
Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head



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 and was given along with an overall assessment. 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 overall assessment and the following grades:

- Grading table of the unit: Promoting Reasearch Oriented Towards Eraly Cns Therapies

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

- Grading table of the team: Pathophysiology and therapy of mitochondrial diseases

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

- Grading table of the team: Developmental vulnerability, innovative evaluation methods, and neuroprotection of the immature brain

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

- Grading table of the team: Genetic disorders of the developing brain

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

Evaluation report

Unit name:	Promoting Reasearch Oriented Towards Eraly Cns Therapies
Unit acronym:	PROTECT
Label requested:	UMR University Paris 7 – Denis Diderot, Inserm and CNRS
Present no.:	UMR 676
Name of Director (2012-2013):	Mr Pierre GRESSENS
Name of Project Leader (2014-2018):	Mr Pierre GRESSENS

Expert committee members

Chair:	Ms Colette DEHAY, Stem Cell and Brain Research Institute, INSERM
Experts:	Mr Patrick BERQUIN, Neurologie Amiens (Representative of CNU)
	Mr Bernard DAN, Neurologie, HUDERF, Brussels, Belgium
	Mr Charles FFRENCH-CONSTANT, Scottish Centre for Regenerative Medicine, England
	Mr Andre M. GOFFINET, University of Louvain, Belgium
	Mr Wolfram S. KUNZ, Abt. Neurochemie Klinik für Epileptologie und Life & Brain Center Universitätsklinikum Bonn Sigmund-Freud, Germany
	Ms Stefania MACCARI, Université Lille 1 (Representative of CoNRS)
	Mr Frédéric SAUDOU, Signalling neurobiology and cancer, Institut Curie Orsay (Representative of INSERM CSS)
	Mr Pierre SZEPETOWSKI, Institut de Neurobiologie de la Méditerranée (INMED)

Scientific delegate representing the AERES:

Mr Yves TROTTER

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

Ms Christine CLÉRICI, University Paris-Diderot

Mr Etienne HIRSCH, Inserm

Mr Bernard POULAIN, CNRS

1 • Introduction

History and geographical location of the unit:

The UMR 676 is an Inserm Unit, located in the Hôpital Robert Debré. The research laboratories (2,000 m^2) are located on the 3rd and 4th floors of the Ecran building of R. Debré Hospital (linked to the main building of the hospital by skywalks).

The main research axis of the UMR 676 "Pathophysiology, functional consequences and neuroprotection of disturbances of the developing brain" is the understanding of the pathophysiological mechanisms underlying diseases of the developing brain, with the objective to operate at the interface between basic research and transfer to the clinic. This has been made possible by bringing together researchers from Inserm, CNRS as well as numerous academic physicians from different Departments of the Robert Debré Hospital (Child Neurology and inherited metabolic diseases, Neuropathology, foetopathology, obstetrics, Imaging and Physiology Departments as well as the NICU and PICU and Emergency services). The translational approach benefits from the support of dedicated structures at the Robert Debré Hospital, such as the Center for Clinical Investigation (CIC) and the Epidemiology Center (CIC-EC).

At its creation, the UMR 676 was already directed by the proposed director and was comprised of three teams. During the 2009-present period, there has been a significant increase in the number of scientific and clinic staff. The lab has attracted 3 new groups (i) one PU-PH, Inserm Avenir grant ii) one MCU-PH, Inserm Avenir grant and (iii) a PU-PH. The present organization chart includes therefore 5 teams.

In addition to these 3 new PIs, 6 tenured Inserm and Cnrs researchers (including 1 new recruitment at the CR (Chargé de Recherche) level and two academic medics have joined U676. Five engineers and technicians as well as two secretaries have been recruited at Inserm and one technician has been recruited at Paris Diderot (1).

The unit has been able to establish/update state of the art platforms including (1) A1 and A2 rodent animal facilities, (2) a phenotyping core facility for newborn rodents (awarded the Diderot Innovation Prize (Diderot University and CNRS, 2006), an Apple Research Technology Support award (2007), and the Inserm Innovation Prize (2010), (3) High-throughput screening for neuroactive small molecules in zebrafish ;(4) In vivo multimodal imaging of foetuses and newborn rodents; (5) Cellular imaging core facility, (6) Molecular biology core facility, (7) Biochemistry core facility, (8) Blood-brain barrier (BBB) evaluation core facility (a component of NeurATRIS (Translational Research Infrastructure for Biotherapiesin Neurosciences, CEA, and supported by ANR).

Two start-ups are being hosted on the research site (1) Mitologics S.A.S., a biotechnology company specialized in the detection of mitochondrial alterations, in collaboration with the Rustin team. (2) PhenoPups a spin-off of the unit launched in 2012, which has strong links with the Gallego team.

Management team:

The proposed director is a director of research at Inserm who has multiple managements responsabilities as Coordinator of the PROTECT Department (DHU), Robert Debré Hospital; Co-director of the PremUP Foundation; Co-director of the International Associated Laboratory Inserm-IISC, Paris-Bangalore. He also acts as a Consultant for the Pediatric Neurology Service of the Robert Debré Hospital and is Professor of Neonatal Neurology, KCL, London, UK. He has been recently awarded the Roger de Spoelberch Foundation award for Research in Neuroscience (2010).

His previous management of U676 has proven to be efficient in promoting the growth of the lab, by attracting new teams and researchers and in establishing technological platforms and industrial partnerships.

The new organization chart corresponds to 3 teams, including 2 large teams that each harbours several subgroups with identified subgroup leaders. This organisation is designed to provide the subgroups with a secure environment in order to promote their future autonomy. This organisation meets the keen approval of the subgroups PIs.

The management structure has been clearly described: the director of U676 acts as the representative of the laboratory and of the executive committee with respect to the supervisory organizations. The decision-making body of the laboratory is the Executive committee, which is composed of the leaders of the teams. The focus is put on consensus, with a clear concern to promote the collective interest. This is exemplified by the budget management policy which requires that 10% of the external grant budget from all teams be pooled in order to finance activities of general interest.

The laboratory council, composed from half by statutory members and half by elected members, acts as an advisory board and gives its views on the decisions of the Executive committee. In agreement with Inserm regulations, the elected members are representatives of the researchers (3/6), of the ITA personnel (engineers/technicians; 2/6) and of the students (1/6).

The PhD students and postdocs appear to be well integrated. They have very good interactions with their supervisors and with the PIs, and showed a good team spirit.

The technical staff, Inserm or universities, is made up of more than 20 members. They are happy to be an integral part of this laboratory and feel involved in the experiments.

Overall, the gouvernance appears excellent, the organisation efficient and collegial, the atmosphere studious, consensual and friendly.

U676 benefits from the scientific council of the DHU (Département Hospitalo-Universitaire), to which the laboratory belongs. This scientific council consists of 5 international experts. The scientific council evaluates the scientific projects of the groups and advises the director and the executive committee. It is planned that the scientific council will be invited to a scientific day of the DHU every two years.

AERES nomenclature:

SVE / SVE1 Biology, health / SVE1_LS5 Neurobiology

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	28 (14 FTE)	32 (16 FTE)	32
N2: Permanent researchers from Institutions and similar positions	13 (13 FTE)	15 (14.5 FTE)	15
N3: Other permanent staff (without research duties)	18 (18 FTE)	20 (20 FTE)	20
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	0	0	0
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	18 (18 FTE)	15 (18 FTE)	15
N6: Other contractual staff (without research duties)	8 (2 FTE)	5 (2 FTE)	5
TOTAL N1 to N6	85 (57 FTE)	87 (70.5 FTE)	87

Percentage of producers	***100 % for N1 to N6 / 100 % for N1, N2, N4 and N5***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	13	
Theses defended	24	
Postdoctoral students having spent at least 12 months in the unit*	18	
Number of Research Supervisor Qualifications (HDR) taken	5	
Qualified research supervisors (with an HDR) or similar positions	33	37

2 • Assessment of the unit

Strengths and opportunities:

- Dynamic leadership by a highly driven and committed director, who is a well-recognised neuroscientist in his field (H factor 42);
- Unique configuration and expertise at the interface between basic and clinical research,
- Strong links with the Robert Debré Hospital,
- Creation of the DHU, a unique translational structure to promote bilateral transfer between basic researchers and clinicians, in addition to the Center for Clinical Investigation (CIC) and the Epidemiology Center (CIC-EC);
- Important cohorts,
- Implementation of several clinical trials,
- Innovative technological platforms,
- Good capacity to obtain external funding,
- Industrial partnerships and patents,
- The proposed organigram includes 3 teams with 2 large teams composed of subgroups. This organisation corresponds to a well thought-of plan to allow a few subgroups to emerge within the next 5 years, while providing them with a secure, consistent transitional environment;
- Ambitious, innovative and promising project with far reaching objectives aimed at implementing high level translational research in neuroprotection of the preterm and neonate.

Weaknesses and threats:

- Limited recruitment of young tenured researchers,
- lack of in-house expertise in bio-informatics,
- some projects on neurogenetics are highly competitive.

Recommendations:

- The unique configuration of the unit at the interface between basic research and clinic should be exploited to attract young team leaders (ATIP/AVENIR) or young scientists via the “ANR retour” postdoctoral programs, who will eventually build their own teams.

- The committee feels that it will be of strategic importance to increase the expertise in bio informatics within the unit rather than through external collaboration; this would entail recruiting new staff.

- Cutting edge approaches in cell biology should be sought for to enhance the impact of some basic research projects in competitive areas (neurogenetics).

- In order to enhance the prominence of the unit and solidify its position as a leader in the field via publications in high profile journals, the PIs should focus on a more in-depth analysis of cell and molecular mechanisms.

3 • Detailed assessments

Assessment of scientific quality and outputs:

Altogether the teams have produced a total of 253 publications directly related to the research of U676 during the past 5 years. The total number of U676 publications is >1000. Publications are in basic research journals as well as in medical journals, including journals of very good IF (Brain, Annals of Neurology, PNAS, Journal of Clinical Investigation, Lancet Neurol, Am. J. Respir. Crit. Care Med, etc). A substantial number of articles are co-signed between teams which indicate the high level of synergy which characterises this lab. For instance, Mr Pierre GRESSENS has co-signed 22 out of 33 publications of the Baud Team.

Of note, the Gressens team is publishing proficiently (344 original articles from 2007-2012, out of which 76 correspond to research performed at U676 and are directly related to the unit project, 44 reviews and 19 chapters). The citation index of the leader (H=42) corresponds to a very good track record in the field. 5 patents have been produced by U676.

Twenty four PhD theses have been completed.

Assessment of the unit's academic reputation and appeal:

U676 is a well-known lab, both at the national and international levels. The teams have developed an extensive network of national (44), europeans (26) and international collaborations (24). Several PIs are associated or coordinators of international and national networks. Out of 22 collaborative projects, 3 are financed by FP7 and 14 by ANR.

U676 has organised 21 conferences/symposia since 2008 (including meetings of FP7 consortia).

The unit members are heavily involved in national scientific committees (Inserm, University, Ministry of Health, Ministry of Research). They also participate to the editorial boards of 13 journals (basic and clinical research)

155 invited conferences are listed in Mr Pierre GRESSENS team (including national and international meetings).

U676 has been very active in recruiting new scientists (7) and clinical staff (3) from France.

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

U676 has numerous (15) partnerships with biotechnological and pharmaceutical companies. Industrial collaboration and valorisation of results are very good, with 5 patents filed and 2 start-ups in operation. Ability to rise external, competitive funding (independent from recurrent institutional support) is high.

U676 has also developed strong links with 24 patient associations.

Members of U676 have actively promoted research and public health issues via interviews/articles in wide audience media (L'Express, Libération, France 5 TV, Parents, Canal Plus, La Croix etc).

Assessment of the unit's organisation and life:

A unique and key characteristic in the organization of U676 is its link to the clinical environment of the Robert Debré Hospital. U676 has established state of the art technological platforms from molecular biology to rodent phenotyping, which provide strong and efficient support to a wide range of research activities of the teams.

The management and internal life of the individual research teams appear very good, with a number of regularly organised journal clubs and meetings. U676 sustains regular scientific interactions via a weekly general meeting followed by a seminar given by an external speaker at least once a month. Doctoral students are encouraged to present their projects at these meetings.

Assessment of the unit's involvement in training through research:

U676 has a strong commitment to formal teaching and training through research. Between 2007 and 2012, members of the unit have taught 1,900 hours as part of the medical cursus, 700 hours for postgraduate medical training (DESC, DU and DIU), and 190 hours as part of Master's research programs. They have organised a European Training school in the Diagnostic and Therapeutic approaches in Leukodystrophy. Members of the unit have organised a training course for practicing neuropediatricians.

The unit has 36 members qualified to supervise doctoral students. Five HDRs were obtained during the last 5 years and three are in progress. Between 2007 and 2012, 11 M1 students, 42 M2 students, 9 Engineering School students, 9 Technical University students, 31 PhD students (24 theses defended, including two with a co-advisor from Finland or the USA), and 35 postdocs have been supervised in the unit. These figures are sizeable considering a "full-time equivalent" of 27 researchers.

Assessment of the five-year plan and strategy:

The project aims to be translational, at the interface between basic research and transfer to the clinic. Together with the joint expertise in basic science and in clinical practice, the strong and reciprocal links with the Hospital Robert Debré put U676 in a unique position to achieve an optimal transfer from the bench to the bedside in children and neonates. The proposed organization chart corresponds to 3 teams including 2 large teams. This organization corresponds to a well thought-of plan to allow a few subgroups to emerge within the next 5 years, while providing them with a secure, consistent transitional environment.

4 • Team-by-team analysis

Team 1 : Pathophysiology and therapy of mitochondrial diseases

Name of team leader: Mr Pierre RUSTIN

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	1 (0.5 FTE)	1 (0.6 FTE)	1
N2: Permanent EPST or EPIC researchers and similar positions	4 (4 FTE)	4 (4 FTE)	4
N3: Other permanent staff (without research duties)	1 (1 FTE)	1 (1 FTE)	1
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2 (2 FTE)	2 (2 FTE)	2
N6: Other contractual staff (without research duties)	1 (0.25 FTE)	1 (0.25 FTE)	1
TOTAL N1 to N6	9 (7.85 FTE)	9 (7.85 FTE)	9

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	1	
Theses defended	5	
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	2	2

• Detailed assessments

Assessment of scientific quality and outputs:

Publications from the last 5 years indicate clearly a steady and continuous flow of publications. Team members have signed articles in very good journals with high impact factors as Cell, Cell Metab., Hum. Mol. Genet., Cell Death Diff. The theme of respiratory chain may not be among the most fashionable ones, explaining probably why most publications were not in high priority journals. The theme is very original and the approaches are focused, solid and sound, with a strong focus on in vivo models of mitochondrial diseases in mouse mutants, zebrafish and even more primitive organisms such as Ciona. The developed mouse models with respiratory chain deficiencies and additional allotropic expression of an alternative oxidase from Ciona to recue cytochrome c oxidase deficiency are of high scientific interest. These mouse models might help to solve the controversial issue of mitochondrial and ROS involvement in aging and neurodegeneration. Of specific interest is the hypothesis that there is some action at a distance of triplet amplification in frataxin that leads to downregulation of *PIP5K* and this may have pathophysiological consequences for Friedreich patients.

Assessment of the unit's academic reputation and appeal:

The Rustin team is very well known in France and abroad, as attested by the number of invited talks and conferences attended, as well as the national and international collaborations and participation to European research programs. Dr. Pierre RUSTIN is very well known in the field of mitochondrial research. The papers from his team are very well cited in the mitochondrial community (Dr. Pierre RUSTIN's H index is 60). Dr. Pierre RUSTIN received Doctor Honoris Causa from Tampere University in Finland.

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

It is more difficult to comment on that aspect. Although the program is focused on basic research, Dr. Pierre RUSTIN and his collaborators have an eye on translational research, aiming to develop new potential pharmacological approaches and innovative technological advances, particularly on mitochondrial disorders and Friedreich ataxia. Of course, how to translate efficiently their basic discoveries into clinically useful technology remains unclear, but the project shows that investigators bear that aim consistently in mind. As example they participate in a treatment study of Friedreich's ataxia with pioglitazone, a PPAR gamma agonist, at the R. Debré Hospital.

Assessment of the unit's organisation and life:

The investigators have clearly in mind a matricial, efficient and modern organization, with transversal technological platforms supporting research.

They now want to propose a new and simplified organigram in which the research project in the Rustin team and clearly identified and well structured.

Assessment of the unit's involvement in training through research:

Several master students and PhD students work in the laboratories and thus learn how to conduct research on a day by day basis directly. Although they do not appear to run a specific teaching program, members of the team participate in various teaching activities, mostly at the advanced level. They also have optimized links and collaborations with other institutions, mostly in the Paris area but also with some in and out of country. There are close links to the GC2ID doctoral school, weekly unit and team meetings and monthly seminars with invited speakers.

Assessment of the five-year plan and strategy:

The proposed strategy is to focus sharply on mitochondrial dysfunction as pathological factor in various disorders and on development of relevant mouse and zebrafish models. Investigators aim to build on their strongest contributions of the last 5 years, thus consolidating and extending them. They are also keen to investigate uncharted territories, but do so in a careful manner, as befits professional scientists.

Given the pivotal role played by mitochondria in different disorders of the developing brain, the main projects will be to develop and study models of mitochondrial disorders (culture of murine and human cells, zebrafish as well as unique mouse models) and clinical studies of patients with brain disorders of mitochondrial origin. This research will extend from the study of basic mechanisms to clinical trials. The team will combine multiple areas of expertise: mitochondria, caspase-mediated cell death, biochemistry, molecular biology, zebrafish models, neurological diagnosis and follow-up of patients with mitochondrial disorders, and clinical trials, like the pioglitazone trial in children with Friedreich's ataxia.

Conclusion:

- **Strengths and opportunities:**

- Strong international recognition,

- Focused, innovative and original research project,

- Clinical application already adressed,

- Recent recruitement of a young researcher at CNRS who will eventually take the lead at the end of the next five years period, when the senior PI will retire.

- **Weaknesses and threats**:

None identified

- **Recommendations**:

- Given that the theme is very original, the team should aim at publishing in journals of higher IF.

Team 2 : Developmental vulnerability, innovative evaluation methods, and neuroprotection of the immature brain

Name of team leader: Mr Olivier BAUD

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	13 (6.5 FTE)	15 (7.5 FTE)	15
N2: Permanent EPST or EPIC researchers and similar positions	6 (5 FTE)	8 (7 FTE)	8
N3: Other permanent staff (without research duties)	5 (5 FTE)	6 (6 FTE)	3
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	7 (7 FTE)	7 (7 FTE)	5
N6: Other contractual staff (without research duties)	3 (0.75 FTE)	3 (0.75 FTE)	2
TOTAL N1 to N6	34 (24.25 FTE)	39 (28.25 FTE)	33

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	6	
Theses defended	10	
Postdoctoral students having spent at least 12 months in the unit	7	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	20	21

• Detailed assessments

Assessment of scientific quality and outputs:

The research theme is a major public health issue for which progress in basic research and in clinical research, including novel therapeutic approaches, is urgently needed. Overall the research is good and sounds original, with a strong focus on the concept of neuroprotection which this group has refined in the context of early developmental brain damage. The emphasis on inflammatory mechanisms is in keeping with international advances and is appropriately considered in an integrative way. Potentially effective agents can be designed from the better understanding of the physiological processes and then tested using various *in vitro* and *in vivo* approaches - towards the design and improvement of clinical trials. A strong effort is made in the direction of such a translational approach and this should be emphasized. Also the phenotyping platform for newborn rodents and the multidisciplinary approach are strong points. In the past period the research has been published in basic science and clinical journals, including a small number of high impact journals.

Assessment of the unit's academic reputation and appeal:

Members of this team have been involved in scientific networking on a national and international scale. They have got a significant number of clinical and scientific grants including ANR and EC grants. They contribute in various basic science and clinical frameworks (including paediatrics / child neurology, neonatology, obstetrics, neuroimaging, neuropathology, endocrinology or nutrition). They have participated in and/or organized a large number of international scientific meetings. The team's leader has got an impressive number of invited talks and is a member of Plos One editorial board. This team is mainly built from pre-existing entities of the same lab - hence it is difficult to appreciate how attractive this new team will be. Several permanent researchers and/or lecturers as well as two post-docs were recruited in the past period, which renders confident in the future attractiveness of the group.

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

The team has developed partnerships with several pharmaceutical and biotechnological companies. They have also obtained several patents in the last years. They have developed partnerships with support and advocacy groups, such as the "Association des Paralysés de France". They were active in the French Ministry of Research-supported network on prematurity. They have been communicating on their findings or explaining issues pertaining to their research through large-audience media (several major French television channels and newspapers).

Assessment of the unit's organisation and life:

This team was built mainly from two pre-existing groups of the unit - plus a few members coming from other external and internal areas. Previously the PI has been heading one of these two teams - which was of much smaller size. The team is composed of many members and has got several different subprojects that all aim at converging on preclinical applications. The birth of this new team makes it difficult to appreciate the long-term stability of its new organization. Multidisciplinarity aspects and the organic connection with a large paediatric hospital is a strong point.

Assessment of the unit's involvement in training through research:

Scientific training is continuously ensured through formal teaching programme as part of the medical curriculum, postgraduate medical training, Master's research programme as well as through interactive seminars involving members of the units, other units and speakers. The unit has members with HDR, i.e. qualification to supervise doctoral students.

Assessment of the five-year plan and strategy:

The project addresses several, partially related issues. Indeed the different subprojects of the team rely on overlapping concepts and share common therapeutic goals in common. It looks difficult to appreciate how efficient the convergence of new projects with pre-existing ones will be. Also, there are several areas with some confusion, perhaps due to format constraint. Hence the reference to problems characterized as 'neonatal' somewhat contrasts with the unit's fine awareness of developmental processes and their expertise with preterm birth.This characterization poses the risk of overlooking the maturational dimension and prenatal processes. The implication might be that the eventual suggestion of intervention strategies in humans based on the research results might be presumed to concern primary prevention while they actually concern secondary prevention. As another example, the reference to *status epilepticus* bears little relevance to neonatal medicine. Having said that, the overall strategy looks appropriate and realistic. Deciphering some of the physiological aspects of vulnerability and neuroprotection in the immature brain is necessary before the appropriate therapeutic options can be designed and tested. The multidisciplinary approach that is proposed fits well with the overall aim.

Conclusion:

- **Strengths and opportunities**:

- international recognition of the PI,
- innovative projects in basic and translational research of vulnerability factors and neuroprotective opportunities in early brain maturation,
- unique phenotyping platform for newborn rodents,
- strong links with the clinicians at the Hôpital Robert Debré,
- ongoing clinical trials,
- links with biomedical companies.

- **Weaknesses and threats**:

The team has a tendency to propose widespread projects. The risk there is that this could result in the different projects not being investigated with sufficient in-depth approaches, which would be counterproductive to ensure the highest impact and visibility of the work.

- **Recommendations**:

So as to optimise the impact of research, the committee recommends that the PI prioritises on the neuroinflammation axis. The project would greatly benefit from collaborations with macrophages biologists.

The impact of the team’s results would be enhanced if the action mechanisms of the drugs used in clinical trials were deciphered at a finer level.

Team 3 : Genetic disorders of the developing brain

Name of team leader: Mr Pierre GRESSENS

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	14 (7 FTE)	16 (8 FTE)	16
N2: Permanent EPST or EPIC researchers and similar positions	4 (3.5 FTE)	4 (3.5 FTE)	4
N3: Other permanent staff (without research duties)	3 (3 FTE)	3 (3 FTE)	2
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	9 (9 FTE)	9 (9 FTE)	8
N6: Other contractual staff (without research duties)	4 (1 FTE)	4 (1 FTE)	2
TOTAL N1 to N6	34 (23.5 FTE)	36 (24.5 FTE)	32

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	6	
Theses defended	9	
Postdoctoral students having spent at least 12 months in the unit	9	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	11	12

• Detailed assessments

Assessment of scientific quality and outputs:

Publications from the last 5 years indicate clearly a strong impact of some projects, particularly those dealing with VIP (maternal factor), a theme of interest of Dr Pierre GRESSENS for many years, and physiopathology of hypoxia-related lesions and white matter insult following inflammation. This clearly points to strength of the group in the physiopathological role of hypoxia, inflammation and neuromodulators, and to their interest in linking basic science to the clinic. In comparison, the theme of neurogenetics was more recently initiated and is still at the maturation stage although the senior investigator leading this new team, like Mr Pierre GRESSENS, has an excellent track record and is an international leader in her field.

Assessment of the unit's academic reputation and appeal:

The Gressens team is well known in France and abroad, as attested by the huge number of invitated talks and conferences attended, as well as the many collaborations nationally and internationally, such as participation to European programs. As judged by leadership of important and influential European networks the senior investigator leading this new team also has an excellent scientific reputation.

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

It is more difficult to comment on that aspect. Being close to the clinic in the environment of a large university hospital, the impact of the work on patients is clearly a major concern of Dr Pierre GRESSENS, and his colleagues. They are heavily focused on translational research, aiming to develop new potential pharmacological approaches and innovative technological advances. Of course, how to translate efficiently their basic discoveries into clinically useful technology remains unclear, but the project shows that investigators bear that aim consistently in mind. Certainly, the collection of large well phenotyped patient cohorts by both investigators (in microcephaly and leucodystrophy) will be of great value and has the capacity to have a major long term impact.

Assessment of the unit's organisation and life:

All principal investigators in this quite large but somewhat heterogenous group have obviously thought a lot about organizing their life and research in an efficient manner. Over the last 5 years, the organigram was more complex than their proposed new version, which should prove more efficient in terms of decision making.

The investigators have clearly in mind a matricial, efficient and modern organization, with transversal technological platforms supporting research. The organizational plan that they propose is elaborate and impressive. A key strength in the organization is the link to the hospital and the clinical environment therein. It would have been helpful to have more detail on interactions with the advisory committee.

Assessment of the unit's involvement in training through research:

Several master students and PhD students work in the laboratories and thus learn how to conduct research on a day by day basis directly. It appears that 35 qualified staff have trained 24 students between 2007-2012. There is however a lack of detail about other aspects of their training - they do not appear to run a specific teaching program. A key metric for a translational unit is the scientific training of clinicians, but no details are provided - we would like to have known how many of the PhD students and post docs are clinically active.

In addition to students working in their laboratories, members of the team participate in various teaching activities, mostly at the advanced level. They also have optimized links and collaborations with other institutions, mostly in the Paris area but also with some centers, in and out of France.

Assessment of the five-year plan and strategy:

The proposed strategy is to focus on three main projects that reach quite widely, although they appear to be well integrated. By doing so, the investigators aim to focus on their strongest contributions of the last 5 years, thus consolidating and extending their contributions. They are also keen to investigate uncharted territories, but do so in a careful manner, as befits professional scientists.

The new organigram, with 3 main groups under leadership of senior investigators should prove more efficient that the previous one, which was more widely spread. This will facilitate integration of new investigators into existing structures, as well as communication and decision making. Specifically, this team will concentrate on **genetic disorders of the developing brain**, with special emphasis on primary microcephalies and cerebellar hypoplasia of genetic origin, on leukodystrophies, and on neuroendocrine control of puberty onset**.** They will combine member's expertise in child neurology, clinical and molecular genetics, endocrinology, imaging, neuropathology and embryonic stem cells and iPS. Their research will aim to identify genes in patients, to develop appropriate experimental models to study pathophysiological mechanisms and to develp neuroprotective strategies. The sharing of technology such as next generation sequencing, mouse and zebrafish genetic engineering will be optimized via platforms.

This proposed team, which will bring together a group with expertise in microcephaly and in the relationship between brain inflammation and perinatal pathology and a group with expertise in axoglial interactions implicated in leucodystrophies, is very logical. We anticipate that it will result in a very strong scientific team. The added value and synergy will be very high if appropriately exploited. The third group of the team (genetics and physiology of the onset of puberty) has a weaker track record and it is also less clear how the work will add value to a focus on perinatal growth and pathology created by the other two PIs - the case for scientific synergy is not expilicitely made.

Three other comments on future plans: First, the committee would have liked to see a clear mechanism to promote collaborations between the groups, and the number of genuine joint publications should be a key future metric. Second, as stated above, an explicit plan to increase the scientific training of young clinicians is required. Third, given that the aim is to understand and treat human pathology, a greater inclusion of human tissue and cells in the early stages of each project would strengthen the proposal. The use of iPS-derived neural stem cells and human tissue for neuropathology studies can now guide mouse experiments, rather than vice versa, with the mouse now used as a translational model to test hypotheses rather than a discovery tool. The unit is extremely well placed to genuinely link the clinic and the lab, and it would be an opportunity lost not to do this.

Conclusion:

- **Strengths and opportunities**:

- The director of the team benefits from an excellent international recognition in the field, with an impressive track-record in the clinical neurodevelopmental domain. He has a proven capacity to foster translational research projects.

- Strong links with the Hopital Robert Debré. The director has developed a remarkably efficient strategy via the creation of the DHU to enhance synergies between basic science and clinical research.

- Well thought of organisation of the team where subgroups leaders can work efficiently so as to build up their future autonomy.

- Some senior PIs of the team have an excellent track-record combined with international recognition,

- Important role of the team in major European networks (eg. in Leukodystrophy),

- Unique cohorts managed and established by team members,

- Outsanding rates of publication in both basic and clinical journals,

- Strong partnership with industry,

- High level of funding,

- Ambitious, innovative and promising project, in both basic and translational research,

- The team is leading clinical trials.

- **Weaknesses and threats**:

- Lack of in-house expertise in bio-informatics,

- Some projects on neurogenetics are highly competitive.

- **Recommendations**:

- Cutting edge approaches in cell biology should be sought for to enhance the impact of some basic research projects in competitive areas (neurogenetics).

- Attract new junior researchers.

5 • Conduct of the visit

Visit date:

Start: Friday, 18 January 2013 at 8h30

End: Friday, 18 January 2013 at 18h15

Visit site:

Institution: Inserm U676

Address: Hôpital Robert Debré

48, Bd Sérurier

75019 Paris

Specific premises visited:

Conference Room, laboratories at the 3d and 4th Floor of the ECRAN building of the Robert Debré Hospital.

Conduct or programme of visit:

The director presented the general organization of the unit and the research organisation and policy, in the presence of all the members of the unit. Then, the committee listened to 20-25 min présentations by each candidate group leader, followed by 20-25 min questions. These evaluations of the teams were conducted in the presence of the whole unit. The committee had the opportunity to visit the laboratory and some existing technical facilities. Three subgroups from the committee had meetings with (i) the students and postdocs, (ii) scientists with permanent positions, and (iii) technical staff. The committee had also a 40 minute exchange with representatives of the «Tutelles»

Representatives of the tutelles :

- Dr Bernard POULAIN , co-director for CNRS of the ITMO Neuroscience
- Dr Etienne HIRSCH, co-director for Inserm of the ITMO Neuroscience
- Professeur Benoit SCHLEMMER, Doyen, Faculté de Médecine Paris Diderot
- Professeur Christine CLERICI, Vice-Présidente, Université Paris Diderot
- Ms Christine GIRIER, directrice, hôpital Robert Debré
- Professeur Jean-Claude CAREL, Président CMEL, hôpital Robert Debré

Ms Sabrina SHANOUN, représentante (responsable RH) de Ms Laurence LOMME, Déléguée Régionale, Inserm Délégation Régionale PARIS 7

Of note, the tutelles were unanimous in declaring their strong support to U676. U676 appears of strategic importance for Inserm in the field of clinical developmental neurobiology. The Hopital Robert Debré declared its strong interest and will to maintain and further expand its partnership with U676 , which is a source of invaluable benefits for clinical research. A telling example of the strong support from the Robert Debré Hospital is the creation of the DHU. Paris Diderot University and paris Diderot Medical School also declared strong support, via funding and attribution of MCU-PH and technical staff positions.

8h30-9h00	Door closed meeting - Presentation of AERES to the committee by the '*Scientific Delegate*'
9h00-9h15	Presentation of the committee and presentation of AERES by the '*Scientific Delegate*'
9h15-10h	Presentation of the UMR 676, scientific assessment and projects: PROTECT (Mr Pierre GRESSENS)

Team presentations

10h-10h45	Scientific assessment and projects, team1: Pathophysiology and therapy of mitochondrial diseases (Mr Pierre RUSTIN)
10h45-11h	***Break***
11h-11h45	Scientific assessment and projects, team2: Developmental vulnerability, innovative evaluation methods, and neuroprotection of the immature brain (Olivier Baud)
11h45-12h30	Scientific assessment and projects, team3: Genetic disorders of the developing brain (Mr Pierre GRESSENS)
12h45-14h	***Lunch***

Meeting with permanent and non permanent staff

14h -14h45	**Meeting with the technical staff** *Audience: members of the committee and Scientific Delegate AERES, ITA representatives of the organisms* **Meeting with PhD students and Post-docs and/or fixed-term contract researcher, engineers.** *Audience: members of the committee, Scientific Delegate AERES* **Meeting with researchers, teacher and researchers** *Audience: members of the committee, Scientific Delegate AERES*
14h45-15h	***Break***
15h-15h45	**Meeting with the representatives of the institutions** *Audience: members of the committee, Scientific Delegate AERES*
15h45-16h15	**Meeting with the head of the UMR** *Audience: members of the committee, Scientific Delegate AERES*
16h30-18h30	**Door closed meeting** *Audience: members of the committee, Scientific Delegate AERES*

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

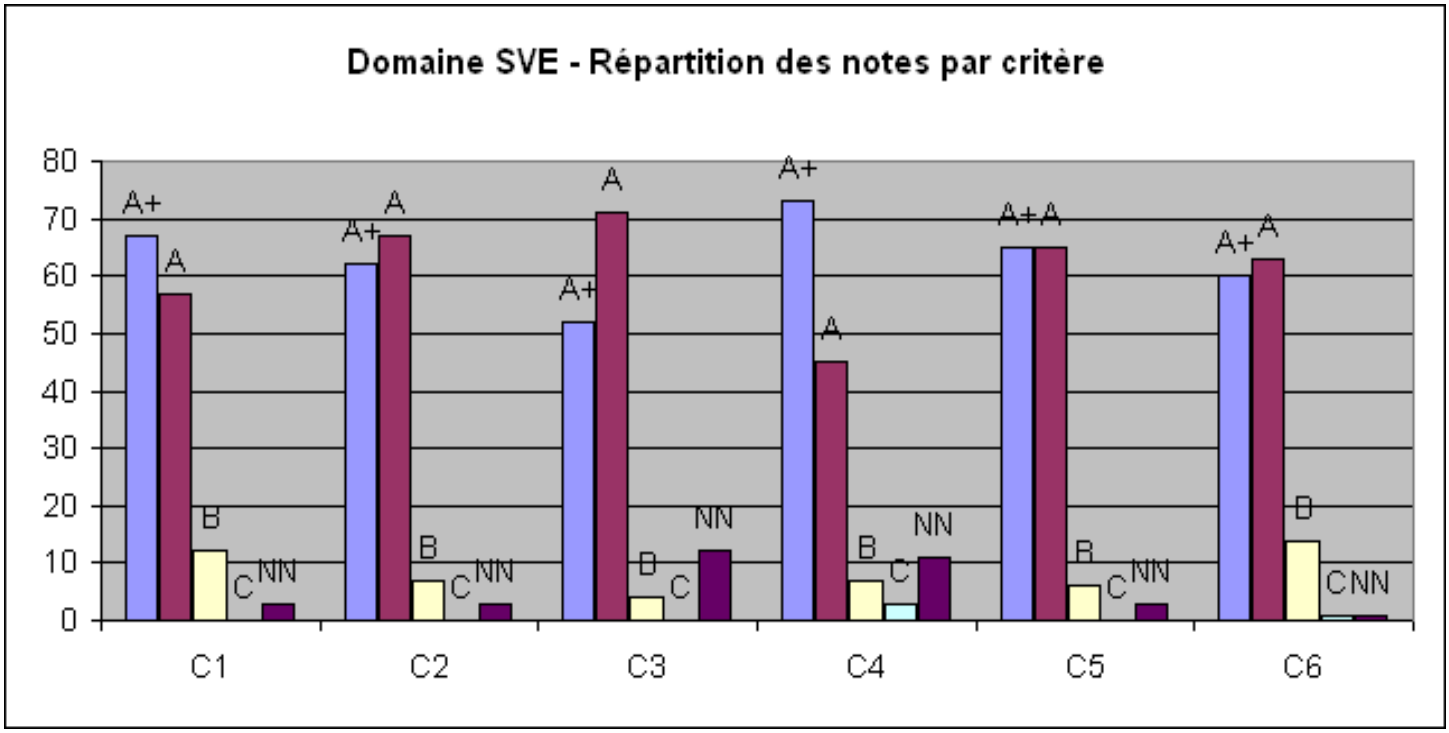
Grades

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

Le Président

P/VB/LB/NC/YM – 2013 - 112
Paris, le 18 avril 2013

M. Pierre Glaudes
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

S2PUR140006382 - Promoting Research Oriented Towards Early Cns Therapies - PROTECT - 0751723R

Monsieur le Directeur,

Je tiens en premier lieu à remercier les membres du comité de visite de l'AERES pour la production du rapport sur la situation de l'UMR 676 « Promoting ResearchOriented Towards Early CNS Therapies »».

Le comité a relevé le très bon niveau de publication et une visibilité importante au niveau national et international, ce dont je me réjouis.

Je suis en accord total avec le comité sur l'intérêt manifeste que représente l'association des organismes de recherche, CNRS et INSERM et de l'Université, des cliniciens et des chercheur.e.s et enseignant.e.s chercheur.e.s. Les capacités à développer la recherche translationnelle est des points forts de l'unité. La position unique de ce laboratoire sur cette interface « basic research/clinic » dans le domaine de la compréhension des mécanismes pathophysiologiques sous-tendant les maladies de développement du cerveau, devrait être indéniablement un facteur d'attractivité pour de jeunes chercheur.e.s

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

Vincent Bergeron

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SORBONNE PARIS CITÉ
RECHERCHE ENSEIGNEMENT SUPÉRIEUR

Paris, le 06/04/13

Comments on the AERES report on unit PROTECT

1. Assessment of the unit

- The unique configuration of the unit at the interface between basic research and clinic should attract young team leaders (ATIP/AVENIR) or young scientists via the "ANR retour" postdoctoral programs, who will eventually build their own teams.

This is part of our strategy to strengthen our unit and expand our fields of expertise, with space and money allocated to such projects for new young investigators.

- The committee feels that it will be of strategic importance to increase the expertise in bio informatics within the unit rather than through external collaborations; this would entail recruiting new staff.

The unit, in conjunction with the DHU, has decided to allocate money to recruit one new staff member with a strong expertise in bio informatics. In future grant applications, salary will be requested for additional staffs with bio informatics expertise, allowing to progressively strengthen our in-house bio informatics expertise.

- Cutting edge approaches in cell biology should be sought for to enhance the impact of some basic research projects in competitive areas (neurogenetics).

Through a combination of in-house developments and selected collaborations with experts in developmental neurobiology (Sonia Garel, ENS, Paris; Corinne Houart, KCL, London), we are currently establishing advanced cell biology approaches in order to strengthen our position in the field.

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- In order to enhance the prominence of the unit and solidify its position as a leader in the field via publications in high profile journals, the PIs should focus on a more in-depth analysis of cell and molecular mechanisms.

As reflected in the more recent publications of the unit, this approach has been implemented in all the teams and will be further strengthened in the coming years.

2. Assessment of Team 1

- Given that the theme is very original, the team should aim publishing in journal so higher IF.

This is the strategy currently developed in the team.

3. Assessment of Team 2

- So as to optimize the impact of research, the committee recommends that PI prioritises on the neuroinflammation axis. The project would greatly benefit from collaborations with macrophages biologists.

We agree with the committee that research on translational neuroprotection should be focused on a limited number of specific mechanisms rather than too widespread approach. However, we have to note that perinatal brain damage is actually not related to only one pathway but is the consequence of combined mechanisms, including neuroinflammation, oxidative stress and excitotoxicity. Nevertheless, in order to ensure high impact publications, our research will be focused on neuroinflammation and in-depth analysis of its cellular and molecular mechanisms.

For what concerns the expertise on macrophages, we have established a collaboration with Michel Mallat (ICM, Paris) and we are currently exploring a potential collaboration with Frederic Geissmann (KCL, London).

- The impact of the team's results would be enhanced if the action mechanisms of the drug used in clinical trials were deciphered at a finer level.
As part of our current research project, drugs targeting oligodendrocyte maturation and microglial activation will be explored in terms of detailed molecular mechanisms of action.

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4. Assessment of Team 3

- Cutting edge approaches in cell biology should be sought for to enhance the impact of some basic research projects in competitive areas (neurogenetics).
Through a combination of in-house developments and selected collaborations with experts in developmental neurobiology (Sonia Garel, ENS, Paris; Corinne Houart, KCL, London), we are currently establishing advanced cell biology approaches in order to strengthen our position in the field.

- Attract new junior researchers.
This is part of our strategy to strengthen our team and expand our fields of expertise, with space and money allocated to new young investigators.

Professeur Pierre Gressens
Directeur UMR 676

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