Laboratoire de neurosciences expérimentales et cliniques

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Experimental and Clinical Neurosciences Laboratory

From the

Université de Poitiers

INSERM

CNRS

December 2010

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

Section des Unités de recherche

AERES report on the research unit

Experimental and Clinical Neurosciences Laboratory

From the

Université de Poitiers

INSERM

CNRS

Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

December 2010

Research Unit

Name of the research unit: Experimental and Clinical Neurosciences Laboratory

Requested label: UMR_S INSERM, UMR CNRS

Name of the director : M. Mohamed JABER

Members of the review committee

Committee chairman

M. Jacques EPELBAUM, Université Paris Descartes

Other committee members

M. Denis HERVE, Institut du Fer à Moulin, Paris
M. Stéphane HUNOT, Institut du Cerveau et de la Moelle
Ms. Brigitte ONTENIENTE, I-STEM, Evry
Ms. Isabelle DUSART, Université Pierre et Marie Curie, Paris (CNU member)
Ms. Stefania MACCARI, Université de Lille 1 (CoNRS member)
M. Marc SAVASTA, Institut des Neurosciences, Grenoble (CSS INSERM)

Observers

AERES scientific advisor

M. Christian GIAUME

University, School and Research Organization representatives

M. Alexis BRICE (ITMO Neurosciences, Psychiatrie, Sciences Cognitives, Inserm)
Ms. Catherine LABBE (Inserm)
Ms. Nathalie LERESCHE (CNRS)
M. Jean-Pierre DEWITTE (CHU)

Report

1 • Introduction

- Date and execution of the visit:

January 12th 2011 from 9h30 to 17h45

General presentation of the LNEC project

Presentation of Translational Projects

Presentation of past activity and projects by team leader 1: Cell Therapies in Brain Diseases

Presentation of past activity and projects by team leader 2: Molecular Targets and Therapy in Alzheimer's disease

Meeting with the Institution representatives

Presentation of past activity and projects by team leader 3 : Neurobiology and Neuropharmacology of Addiction

Presentation of past activity and projects by team leader 4: Psychobiology of Compulsive Disorders)

Three meetings in parallel with permanent scientists, technicians, students and postdocs.

Door-closed meeting: Committee members, AERES representative

- History and geographical localization of the research unit, and brief presentation of its field and scientific activities

The "Laboratoire de Neurosciences Expérimentales et Cliniques" (LNEC) is located within the « Biologie--Santé » project of the Poitiers University. From 2006 to 2010 LNEC members were in: 1) a research group led, and an Inserm Avenir starting grant, both inside the « Institut de Physiologie et Biologie Cellulaires (IPBC) - UMR 6187 » , and 3) a university team (« Groupe de recherche sur le vieillissement cérébral (GREVIC) - EA 3808 »). Clinicians participating to LNEC are also members of an Inserm-«Centre d'Investigation Clinique». During the same period, two full time scientists (1 CR Inserm with a Avenir starting grant and 1 CR CNRS) and 5 assistant professors were recruited. 1 associate professor was promoted to professor, 3 clinical assistant professor and professors were recruited/promoted and 4 technicians or engineers were recruited.

In the past period, scientists of this future unit have made major scientific contributions:

- in damaged adult brain, transplanted embryonic and stem cells derived neurons can extend long distance axons to target remote brain regions (Nature, Nature Neurosciences, TINS…)
- positive life experiences can be beneficial in preventing and treating drug addiction (PNAS, Neuropsychopharmacology, Progress Neurobiol…)
- novel pharmacological agents help treating drug addiction (J Neurosci., CNRS patent…)
- functional role for intrastriatal dynamic circuitry in addiction (Neuron)
- etiological factors of vulnerability to drug addiction (Science)
- apoptotic mechanisms induced by PKR activation in different models of Alzheimer's disease (AD) and in AD patients peripheral monocytes (JCMM, JBC, Neurobiol. Aging, Neurobiol Dis)
- PKR involvement in amyloid- or stress-induced inflammatory processes (JAD, JPET).

- Management team

One Director and oneDeputy-director and coordinator of translational research

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	17	18
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	4	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4	4
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	6	6
N7: Number of staff members with a HDR or a similar grade	9	11

2 • Overall appreciation on the research unit

- Summary

This is an excellent unit in the field of preclinical neurosciences, particularly in the field of addictive behaviors and brain repair.

- Strengths and opportunities

- Charismatic leader who succeeds in building up a scientifically coherent unit from its own small CNRS team and an existing University unit.
- High impact publications in three out of 4 teams despite, for some of them, heavy teaching and clinical loads.
- Ability to recruit young promising investigators
- Excellent laboratory facilities (in particular for animal experimentation)
- Excellent translational facilities to the clinics
- Strong support from local and regional institutions

- Weaknesses and threats

- Find a way to cope with the high teaching and clinical loads
- Increase technical and administrative staffs
- Increase PhD student number

- Recommendations

- Continue to strengthen the translational approaches with the CIC.
- Find a way to balance financing between teams

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	All
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	All
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	1
A4: Number of HDR granted during the past 4 years	4
A5: Number of PhD granted during the past 4 years	10

3 • Specific comments

- Appreciation on the results

The unit brings together 4 teams with strong expertise in a broad range of research topics. The four teams develop pertinent researches in their own field. Three out of the four teams do it with a high international impact.

Overall, the various teams present an excellent track record in term of publications. From 2006 to 2010 LNEC members published 87 basic (4 in the top 1% and 12 in the top 10%) and 57 clinical (4 in the top 1% and 12 in the top 10%) articles with 7 citations in the Faculty of 1000 Medicine and 5 in Faculty of 1000 Biology

Invited seminars: team 1 4 in France; Team 2, 8 in France 3 in Europe; Team 3, 2 in France; Team 4, 3 in France, 2 in Europe, and 3 in the USA.

- Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners

The various PIs are quite well known in France and some can be considered as leaders at international level in their domain as indicated by awards and invitations to seminars and reviews

Oral presentations: Team 1, 2 in France, 2 in Africa, 1 in Europe and 5 in France, 2 in Africa, 2 in Europe, 2 in the USA; Team 2, 3 in France, 1 in Europe ; Team 3: 1 in France, 1 in Africa, 2 in Europe, 1 in the USA ; Team 4: 4 in Europe, 1 in USA

Awards

2007: FENS Scientific Highlight of the year based on Nature Neurosciences article;

2008: European College on NeuroPsychopharmacology (ECNP) Fellowship award;

2009: Award from the Institut de France and EBPS Young Scientist award.

As developed in the individual team reports, the unit as a whole was quite successful to recruit high-level post doctoral fellows in team 1, 3 and 4.

There is a wide range of success to grant applications from rather impressive (team 4) to very good (team 1) and average (teams 2, 3).

This is the case for team 4 that is affiliated to Cambridge University as “Laboratoire Européen Associé” (LEA) and team 1 which developed a long-lasting collaboration with an excellent laboratory from Brussels.

The communicative abilities of the unit are excellent as assessed by a number of national media shows, and, at international level, by several press releases following publications. The relationships with the private sector should be strengthened.

- Appreciation on the management and life of the research unit

The unit leader has a very clear view of the future of its unit and he has developed the means to reach his goals.

He has extensive expertise in managing and evaluating research projects as attested by his many local, national and international responsibilities (member of the national committee of the CNRS Physiology section 25; former member of the French Neurosciences Society board and member of its election committee; president and member of AERES national evaluation committees in Neurosciences; scientific referee for (i) the French ministry of research and higher education, (ii) the ANR Era-Net Neuron, (iii) the Aquitaine Region and the Neuropole Paris, (iv) the Neurological Foundation-New Zealand and (v) the PD Society-UK). He is also chairing an international cooperation program with Lebanon, involving several teams financed by the French Ministry of foreign affairs and PICS –CNRS and a board member of a large GDRI-CNRS program for cooperative projects with Morocco. He is also a member of the editorial board of the European Journal of Neuroscience.

At the regional level, the unit director is also the head of the CPER « handicap and aging » for the Poitou-Charentes Region (a large program with researchers in all fields working on aging and memory), a member of the scientific board of the doctoral School in Health and Biology, a member of the Master Biology jury and the vice-president of the scientific expertise commission at Poitiers University. He is also an invited member of the scientific council of both the Medicine-Pharmacy and Sciences faculties.

The unit deputy director is a clinician. "Institut Universitaire de France" Junior member, in charge of the Movement Disorder and Neuromodulation Unit of the "Pôle Neurosciences", of the Poitiers CHU and of the Regional Clinical Competence center for the care of patients with Tourette's syndrome, Huntington disease, genetic cerebellar ataxia, multiple system atrophy, progressive supranuclear palsy, progressive aphasia and frontal lobar degeneration syndrome in the CIC Unit 802- INSERM.

The proposed organization clearly reflects the will of the Director and Deputy Director to combine experimental and clinical research, and form an effective and successful structure with strong reciprocical translation. This organization is understood and supported by the entire staff. Active communication and interactions with local partners has resulted in a very performing structure.

Both the unit director and his deputy director are very well accepted by the entire unit. They have carried out a clear and convincing reorganization of all the neuroscience teams in Poitiers University. The teams 1, 3 and 4 are in the direct continuity of previous research groups. The team 2 appears to have undergone a profound reorganization with a change in team leader. Although the new team leader appears perfectly competent in her research domain, the new structure still needs to prove its operational capability.

There is definitively a high-level of risks. However, ambition is served by cleverly thought innovative research in 3 out of the 4 teams, and was perceived as a very positive point due to accurately monitored involvement of each member in defined tasks.

All university staff members are heavily involved in teaching in Poitiers University. Clinicians are participating in the Neuroscience and geriatric aspects of the Clinical Investigation Center and the Deputy Director is responsible for the Neuroscience project of the CIC.

- ## Appreciation on the scientific strategy and the project

All the projects as presented in the text and during the site visit can go further than the next four years. The feasibility of the various projects appears real in many instances.

The Unit director is well aware that he will have to regulate the balance of funding between the teams.

Three of the four teams develop original and innovative research in their respective fields.

- ## Conclusion

  - ### Summary

- Extremely favorable

  - ### Strengths and opportunities

- Original projects that include exploratory and more secured aspects
- Complementary skills among members from basic to clinical research
- Active international collaborations found in two of the four teams

  - ### Weaknesses and threats

- Insufficient funding in two of the four teams
- No private funding
- Insufficient administrative and technical support

  - ### Recommendations

An excellent unit that reached the difficult goal of performing top-level research with a heavy teaching load. The reorganization process inside the new unit is encouraged. The Unit should be supported by adjunction of full-time researchers and technicians. PIs which are University professors should get more teaching discharges.

4 • Appreciation team by team

Title of the team 1: Cellular Therapies in brain disease

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	1
N7: Number of staff members with a HDR or a similar grade	1	2

- Appreciation on the results

This team has, in the recent past, made a number of novel and very important contributions in the field of brain repair. In particular, they have demonstrated the ability of embryonic neurons to establish appropriate connections, even at long distance, in the adult damaged rodent brain (Nat Neurosci). These findings revealed the unsuspected potential of neural cell transplantation to promote reconstruction in adult brain diseases (such as Parkinson). This team also made a very significant contribution to the identification of a novel intrinsic pathway of in vitro differentiation of murine embryonic stem cells into functional cortical neurons (Nature).

They have an excellent publication track record in very high impact factor journals (Nature, Nature Neurosci,) and 15 out of their 18 primary publications are signed in first or last author. 3 PhD students have obtained their thesis. They have established partnerships in France, EU, and Australia. It is a very good example of a "teaching team" (all permanent members belong to University) with high productivity in term of quality.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team is recognized in the neural transplantation community. The team leader participated to international conferences. Two postdoctoral fellows have been recruited in the team during the last "quadriennal" period. Researchers from the team obtained numerous grants in the past (a total of 900 k€ during the last 2 years, corresponding to national grants and one FEDER grant and for the future 1 ANR for 2009-2012). The team leader was a member of the Neuroscience University Council (CNU section 69). She is scientific expert for the Human Frontier Science Program and the STEMPOLE Île-de-France, therefore participating in call implementation.

The team participates in 4 European collaborations, all with published or submitted results. The collaboration with a lab in Brussels has lasted for 4 years and resulted in the Nature publication in 2008. The collaboration with a lab in Cambridge resulted in an article recently published in Hippocampus. Five national and local collaborations are also underway.

- Appreciation on the scientific strategy and the project

The project is in continuity with the previous work of the Team and is developed along several original lines in keeping with the main theme:

- Understanding the importance of pre-transplantation patterning of mouse ESC-derived neural progenitors on the fate and connections established between the host and the graft in the neonatal and the adult rat brain. Intracortical microcircuitry will be evaluated electrophysiologically. Among the three sub-projects proposed, one might be less relevant: the control of cell fusion and teratoma formation following transplantation of mouse-ESC-derived neural progenitors. This debate is behind us and a consensus has definitely been reached on the necessity to acquire a post-mitotic stage of differentiation before transplantation. Fusion between host and grafted cells remains an epiphenomenon and, considering the reduced human forces of the team, might be a waste of time.
- Understanding the role of neovascularisation in the graft development. This is a crucial issue and will bring a valuable set of data to explain graft survival and integration into the host brain.
- Potential of ESC therapy in a rat model of Parkinson's disease. This aim is the most fragile of the three since a number of top international groups compete in the field. However, one of the orientations taken by the Team, the exploration of axonal guidance molecules, remains original and less furiously investigated by others. Inclusion of in vivo imaging in the set of techniques used by the team is quite relevant.

Altogether, the projects are totally pertinent with regards to the expertise and skills of Team 1 members. The feasibility is warranted. Overall, the results should bring valuable data for the understanding and therapeutic use of stem cells. All sub-projects are defined under the frame of a specific grant allocation. This reveals mastering of the budget. New techniques that require non-available materials are developed through appropriate collaborations.

- Conclusion

  - Summary

The group is well funded and internationally recognized and has a clear vision going forward of the work that they want to do. They are well positioned to conduct their work programme. They have developed a highly specificity to conduct in vivo work.

  - Strengths and opportunities

- State-of-the-art technology;
- Original projects that include exploratory and more secured aspects;
- Relevant organization of the sub-projects around financial and human possibilities;
- Complementary skills among members;
- An active international collaboration with a very good group in Belgium.

  - Weaknesses and threats

A bit more implications at the international level

  - Recommendations

An excellent team that reached the difficult goal of performing top-level research with a heavy teaching load. This team should be supported by adjunction of full-time researchers and technicians. University professors PIs should get more teaching discharges.

Title of the team 2: Molecular Targets and Therapy in Alzheimer's disease

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	12	8
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	8	2
N7: Number of staff members with a HDR or a similar grade	7	4

- Appreciation on the results

This team has, in the recent past, made a number of solid contributions in the field of neuronal death controlled by PKR and neuroprotective molecules as well as inflammatory processes in degenerative diseases. These contributions were published in specialized journals and 22 out of 23 were signed in first or last author. The productivity of the group is viewed as good; given the fact that all the team members do have heavy teaching loads.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team is recognized at the national level in its field of research.

- Appreciation on the scientific strategy and the project

The Team is in the process of reorganization inside the new unit with several former members joining other teams. The PI has a good publication track record with several well-cited papers and has shown in the past real team management capabilities.

The project is in continuity with part of the previous work and is developed along two main lines: 1) Chemotaxis between peripheral mononuclear cells and nervous cells (astrocytes or neurons) in Alzheimer's disease (AD); 2) Autophagy and inflammation in AD. While several aspects of the research program are interesting and timely (e.g. the link between autophagy and inflammation) other component projects such as chemotaxis lack originality and suffer from weak strategies to address the issues. In particular, there was a tendency to gloss over problems and limitations of the techniques that were to be used. The autophagy and inflammation project is financed by a 2 year grant from the LECMA foundation (80 k€).

The team is also involved in a national collaboration on inflammation and alpha7 nicotinic receptors in AD and a locally coordinated PHRC is running until 2012 to study the relation between peripheral cytokines and chemokines and cognitive decline in AD patients (66 k€/year).

Altogether, the projects are relevant with regards to the expertise and skills of Team 2 members. Yet, one point to be raised is that the field is a very competitive one and the innovative aspects setting this group apart from others were not completely clear. Moreover, with the noticeable exception of the autophagy one, the projects appear very large for a team of such size, with heavy teaching loads.

- Conclusion :

  - Summary

The group has been formed recently and is in the process of maturation of scientific targets. The projects are funded for the next two years and are being reorganized to better reach their new objectives. They are well positioned to conduct some part of their work programme (see above).

  - Strengths and opportunities

- Translational research;
- Relevant organization of some sub-projects around financial and human possibilities;
- Complementary skills among members;
- Active national collaborations.

  - Weaknesses and threats

- Insufficient recognition at the international level;
- Insufficient funding in regard to the whole extent of the project.

  - Recommendations

A good team in the process of reorganization inside the new unit with a heavy teaching load. The chemotaxis program should be more critically defined and evaluated in terms of methodological approaches. This Team should be encouraged to continue its effort to progress to the international level.

Title of the team 3: Neurobiology and Neuropharmacology of Addiction

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)		
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	2
N7: Number of staff members with a HDR or a similar grade	0	2

- Appreciation on the results

The main subject of the team is to discover therapeutic interventions able to reduce relapse to addiction in abstinent addicts. In clinical practice, stopping drug consumption is obtained relatively easily for a short while but relapse is extremely frequent, the risk remaining very high even after long periods of abstinence. Relapse vulnerability represents the main problem for long-lasting treatment of addiction. Using preclinical approaches, the team explores environmental and pharmacological manipulations that can reduce the risks of relapse. This research subject is extremely pertinent with high clinical importance. The team has operated significant breakthrough during the last years by showing that enriched environment is able to reduce cocaine-induced behavioral changes and cocaine relapse in animal model. This discovery had an important impact in this field of research.

The quality and quantity of scientific production, including a patent application, were extremely good during the last 4 years for a team of that size (14 of the 19 articles were signed in first or last position). The team leader was invited in several meetings, including 2 as chairperson. The team leader has defended his HDR and he has trained 3 PhD students during the four years. His scientific work has led to a patent application.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team leader trained 3 PhD students during the last 4 four years. He has received several awards. His activity had significant impact in the field, as indicated by several invitations to meetings and seminars in Europe, Africa and USA as well as two calls for writing reviews. As indicated on the table, two additional university staff members will join his team. He was also able to attract a very promising scientist who was recruited in Inserm and who rapidly obtained an AVENIR grant and became independent as team 4 of the unit.

- Appreciation on the scientific strategy and the project

Despite an important effort for rising funds, the team only showed a modest success for obtaining grants. However, it has received several small grants from MILDT and NIH as well as regional support. This funding has allowed to set-up valuable equipments for efficient behavioral analysis of drug addiction in rats. This modest success for finding grants has not been a limit to do research of high level until now; thereby confirming the management quality of the Team leader.

The scientific project is pertinent, addressing clearly important issues in the domain of addiction treatment that represents a crucial challenge with the increasing problem of addiction in public health. The team will continue to assess the curative effects of enriched environment on drug addiction. It also wants to find new pharmacological treatments for long-term risks of relapse and develop new neuroprotective strategies against the neurotoxic effects of methamphetamine.

During the last years, the team has built an operative platform for studying biological and behavioral effects of drugs in rodent and the feasibility of the proposed preclinical studies is warranted. However the size of the project is not appropriate to the size of the team and the clinical studies remain to be clarified. Some focussing would help this young and promising investigator to maintain his position at the international level.

- Conclusion

  - Summary

The project is clearly adapted for duration of 4-5 years (probably even more).

Presently, funding appears insufficient but the unit director is willing to support this team. The quality and quantity of recent production indicate that the team will succeed in grant applications in the next years and the funding problems should be solved rapidly. The team would need the recruitment of an additional permanent researcher and the PI is exploring actively possibilities in this domain.

The team is leader in the effects of environmental enrichment on drug abuse and this represents its main originality. The team project takes advantage of this situation and will explore how living in enriched environment can protect against addiction. The third axis in the project is less developed and appears less original than the two others.

  - Strengths and opportunities

- The scientific outcome of the team is very positive particularly regarding the demonstration that an enriched environment is protective and curative against drug effects
- Active team leader, recipient of several international awards
- Several powerful techniques in basic and behavioral neuroscience were developed during the last 3 years.
- The Team recruited an INSERM CR who almost immediately obtained an Avenir grant.

  - Weaknesses and threats

- Low funding.
- Given its size, the project could be more focussed on the strength of the team.

  - Recommendations

- The effort for fund raising has to be pursued to allow team development in good conditions.
- A young, promising and active team.

Title of the team 4: Psychobiology of Compulsive Disorders

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	2
N7: Number of staff members with a HDR or a similar grade	0	2

- Appreciation on the results

The committee decided it was not really useful to reassess the results and production of this AVENIR team that separated from the former group 5team 3) after obtaining an AVENIR team in 2009. The team leader has kept his relationships with Cambridge University and obtained an official collaborative network with this University in 2010.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

This young team leader already had a significant impact in the field, as indicated by several awards and invitations to meetings and seminars in Europe and USA as well as many calls for writing reviews. As indicated on the table, two additional university staff members will join his team, including the deputy director in charge of coordinating the translational research of the unit. He was also able to attract excellent postdoctoral fellows. Since 2010, his team is associated with a Cambridge University laboratory, led by one of the leading pioneer in the field of behavioural neurosciences.

- Appreciation on the scientific strategy and the project

Based on its excellent track record and grant writing abilities, the PI has raised 800 k€ in the last two years (half for equipment and materials and half for salaries). This undoubtedly indicates unique management skills. The fact that two new members joined the Team for the present application is another indication of the PI ability to build an interesting and compelling project.

As already stated, the project has been clearly evaluated as excellent through the AVENIR/ATIPE programme and this has not changed in the last year. The team leader has elaborated a new conceptual framework of addiction based on the formation of "incentive habits" in drug addicts. The team has built a very interesting scientific program including studies in animal and patient that proposes an attractive connection between brain mechanisms of addiction and those of impulsivity-compulsivity disorders. Clinical perspectives on transcranial magnetic stimulation (TMS) of cortex for reducing relapse vulnerability to drug addiction are particularly interesting. The study of deep brain stimulation (DBS) of nucleus accumbens in addiction and impulsivity-compulsivity disorders is also noteworthy.

- Conclusion

  - Summary

The project is ambitious but very well thought with an interesting association of preclinical and translational studies. The team leader is certainly in the best position to fulfil his goal.

The team would need the recruitment of an additional permanent researcher and the PI is exploring actively possibilities in this domain.

  - Strengths and opportunities

- Solid expertise in developing preclinical models and performs Top-Down approaches in the field of obsessive compulsive disorders and addiction.
- Several powerful techniques in basic and behavioural neuroscience developed during the last year
- Success in grant applications, local support and international stature

  - Weaknesses and threats

- Limited management experience;
- Limited size of the team;
- Lack of private fundings.

  - Recommendations

- Continue to develop model-based working hypotheses.
- Focus on a given model of psychiatric disorder.
- Validate the confidence put by publishing shortly “Poitiers-derived” studies.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
LABORATOIRE DE NEUROSCIENCES EXPÉRIMENTALES ET CLINIQUES	**A+**	**A+**	**A+**	**A**	**A+**
PSYCHOBIOLOGY OF COMPULSIVE DISEASES [JABER-BELIN]	Non noté	A+	Non noté	A	A+
CELL THERAPIES IN BRAIN DISEASES [JABER-GAILLARD]	A+	A+	Non noté	A	A+
MOLECULAR TARGETS AND THERAPY IN ALZHEIMER'S DISEASE [JABER-PAGE]	A	B	Non noté	B	B
NEUROBIOLOGY AND NEUROPHARMACOLOGY OF ADDICTION [JABER-SOLINAS]	A	A	Non noté	A	A

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	**42**	**5**	**20**	**26**	**36**	**59**	**5**	**17**	**29**	**239**
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

*** les résultats SVE2 ne sont pas définitifs au 06/05/2011.**

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

- **SVE1 Biologie, santé**
  - **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
  - **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
  - **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
  - **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
  - **SVE1_LS5 Neurosciences**
  - **SVE1_LS6 Immunologie, Infectiologie**
  - **SVE1_LS7 Recherche clinique, Santé publique**
- **SVE2 Ecologie, environnement**
  - **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
  - **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
  - **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

Experimental and Clinical Neurosciences Laboratory (LNEC); Comments, answers and additional information to the AERES evaluation report.

General comments

1. Local context: short reminder.

- The main aim of this new research unit is to put together all teams working in the field of Neurosciences in Poitiers. This interdisciplinary project brings together researchers from different conceptual backgrounds (psychobiologists, cell and molecular biologists, toxicologists, electrophysiologists, neuroanatomists, neuropharmacologists, clinicians…) to provide better understanding and, potentially, new therapeutic approaches to neurodegenerative diseases, addiction and compulsive disorders.
- Four sets of topics have emerged that federate all the research activity in Neurosciences in Poitiers around which four teams were constituted. The structure of the LNEC will be organized in teams largely autonomous, although not isolated, both scientifically and financially. Cross-talk and synergy between teams will be encouraged through, for instance, a priority for PhD fellowships for common projects.
- The LNEC project will be a part of a SFR project (Federative Structure of Research) with the aim of federating all Biology-Health laboratories around common scientific aims (cancer research, canalopathy, pharmacology and neurosciences) and technical facilities. This new SFR should also help increase the visibility of research performed in Poitiers at the local, national and international levels with calls for post-doctoral fellowships and subsequent funding to help install new teams. We will also be a part of a thematic SFR project in Neurosciences at Tours, which will give us access to imaging facilities.

- Poitiers and Tours CHUs (Hospital-University Center) have very close clinical connections. The Neurosciences clinical and pre-clinical activities have been identified as the major elements between these two centers and are considered priorities for future development. Both CHUs have specific grant calls to encourage collaborations between the two centers, and our group has recently received related funding.

2. *Relation with the private sector:* we have several ongoing contracts and collaborations.
    a. Team 1: BIOALTERNATIVES (Gençay-FRANCE) (2009) "In vitro pharmacological tests for the toxicity/safety of various compounds on primary dopamine neurons".
    b. Team 2: BIOALTERNATIVES (2009), "The role of astrocytes in the physiopathology of Alzheimer's disease". Furthermore, the team leader has submitted an ANR MALZ 2011 project with the Bio*alternatives* company as a partner.
    c. Team 3: The team leader is a scientific consultant for the CRO Porsolt Inc.
    d. Team 4: AB Sciences (2011) Identification of potential therapeutic effect of XX on stimulant and opiate addictions: preclinical analysis in the rat. We are also in advanced discussion with a major international pharmaceutical company for a preclinical contract aimed at identifying the potential addictive properties of a phase II molecule.
    e. The Deputy director has recently obtained a major contract (2,4 M€) with ABBOTT pharmaceuticals as he is leading a multicentric investigational trial in the Parkinson's disease domain.

3. *Heavy teaching load, lack of significant number of technical and administrative staff:* we agree with the committee who raised these important points. We hope that when the new laboratory will be labelled, the local and national institution will significantly increase their support. The university has already agreed to allocate a financial manager and a research engineer to the Unit.

4. *Increase PhD student number:* the last three years, every year, 2 PhD fellowships from the French Minister of Research have been allocated to LNEC members. Although we do agree that the number of PhD students should increase, the local doctoral school has been supporting the creation of this new research unit significantly.

5. *The operational capability of team 2:* In the last 5 years, team 2 has had very intensive and fruitful interactions with clinical scientists as attested by:
    a. Several publications in the last 5 years in journals such as JBC, JCMM, JAD, J. Neurochem and NBD. The implication of clinicians in these papers is significant as attested by their signature in first or last position.
    b. Many clinicians from the local hospital have received and receive training in preclinical neurosciences by members of team 2.
    c. Members of this team have been key in putting together and running the CPER project 'aging and handicap" that is led by The Unit director.
    d. In the last 5 years, team 2 have raised 636 000 Euros (LECMA, AIRMA, PHRC CYTOCOGMA, AAP PRES Limousin-Poitou-Charentes, ACI Tours-Poitiers, AAP Biology Health of CHU and Faculty of Medicine and Pharmacy) in addition to three PhD fellowships for young researchers (180 000 Euros).
    e. A PU-PH, within this team, is the PI of a national and multicentric PHRC including a translational axis with the head of team 2.

6. *Balance funding between the teams:* since the AERES visit the management board has been regularly meeting. It is composed of the General Director, Deputy Director and the heads of research teams. Management regulations have already been set and voted for. Among the decisions that have been made, the management board agreed that whenever possible, 10-20% of grant allocations (depending on the type of the grant) and recurrent funding will be withheld by the general director and would be allocated to designated research projects.

Team I: Cell Therapies in Brain Diseases

We would like to thank the committee for its positive evaluation and suggestions. Overall, we are in agreement with the present report and therefore have a limited number of comments.

1. « T*he control of cell fusion and teratoma formation following transplantation of mouse-ESC-derived neural progenitors. This debate is behind us and a consensus has definitely been reached on the necessity to acquire a post-mitotic stage of differentiation before transplantation »*.

We do agree that the risk of teratoma formation may be reduced by prolonged cell differentiation before its engraftment. However, pre-differentiated ESCs or ESC-derived precursor cells might still form teratoma after transplantation into animals as previously reported. From the safety standpoint, and since these are the types of cells that we will be using, we believe that the tumorigenic ability of ESCs should be controlled.

2. *« Potential of ESC therapy in a rat model of Parkinson's disease. This aim is the most fragile of the three since a number of top international groups compete in the field. However, one of the orientations taken by the Team, the exploration of axonal guidance molecules, remains original and less furiously investigated by others. Inclusion of in vivo imaging in the set of techniques used by the team is quite relevant".*

We agree that this is a very competitive field. However we have an international solid reputation in the field of cell therapy in Parkinson's disease as attested by:

(i) The originality of our approach which is based on cell transplantation within the lesioned site, the substantia nigra and not within the target site, the striatum as widely performed currently.

(ii) Our recent invited review in Trends in Neuroscience with the exclusive *Cover* illustration (issue of March 2011).

(iii) The recent acceptance of a FENS Forum 2012 symposium that we proposed in which the team leader is a speaker among three other world renewed speakers in the field of Parkinson's Disease (A Bjorklund, O Isacsson and S Dunnett). The symposium is entitled "Circuitry repair in Parkinson's disease: are we there yet?" and is chaired by the Unit Director.

Team II: Molecular Targets and Therapeutic in Alzheimer's disease

1. *The Team is in the process of reorganization inside the new unit with several former members joining other teams.*

The former members who joined other teams did so because of scientific coherence. They were working on aspects related to Parkinson's disease or Neuropharmacology which fits better with the projects of team 1 and 3 respectively. Two additional researchers will be joining this team by January 2012 among which a young and talented MCU-PH from Limoges working on autophagy in Alzheimer's disease.

2. *The team is also involved in … a locally coordinated PHRC running until 2012 to study the relation between peripheral cytokines and chemokines and cognitive decline in AD patients (66 k€/year).*

As a matter of fact, a PU-PH member of this team is the PI of this national and multicentric PHRC.

3. *The group is funded for the next two years and in the process of reorganization towards the work that they want to do.*

Our research team (previous EA) has a strong translational research activity through the presence of clinicians, pharmacists and scientists. In preparation for the future contract, this team has been restructuring for the last two years at the level of scientific projects, grants and researchers.

4. *There is a wide range of success to grant applications from rather impressive (team 4) to very good (team 1) and average (teams 2, 3)." and "Insufficient funding in two of the four teams".*

Between 2006 and 2010, the GREVIC/team 2 received 636 000 Euros in funding: LECMA, AIRMA, PHRC CYTOCOGMA, AAP PRES Limousin-Poitou-Charentes, ACI Tours-Poitiers, AAP Biology Health of CHU and Faculty of Medicine and Pharmacy. In addition, this team has benefited from three PhD fellowships (180 000 Euros).

5. *There is definitively a very high and clever-thought innovative research in 3 out of the 4 teams of the unit." "Three of the four teams develop original and innovative research in their respective fields".*

Team 2 has a national and international scientific specificity, which is the work on peripheral blood cells of patients with Alzheimer's disease. Exploring the involvement of these cells in the physiopathology of AD is original and innovative, and to our knowledge not investigated by other groups in France. It was a deliberate choice not to detail this project in the AERES document; nevertheless, it has been developed in the project ANR MALZ filed last march with an industrial partner. However, we do recognize that the aims of this project focused on chemotaxis between the periphery and the CNS were not detailed in the document; this was mainly due to lack of space. Nevertheless, these goals are clearly developed in the project ANR MALZ filed last March with an industrial partner (*Bioalternative*-FRANCE). In addition, the evaluation committee has verbally raised the need to strengthen our team with an immunologist. Currently, we are in discussion for a possible integration of two immunologists (MCU-PH and PU-PH) by September 2012.

List of Publications of team 2 since the AERES visit:

1. Noël A, Barrier L, Rinaldi F, Hubert C, Fauconneau B, Ingrand S. Lithium chloride and staurosporine potentiate the accumulation of pGSK3βTyr216 resulting in GSK3β activation in SH-SY5Y human neuroblastoma cell lines. **J Neurosci Res**, 2011 May; 89(5): 755-63.
2. Barrier L, Fauconneau B, Noël A, Ingrand S. Ceramide and related-sphingolipid levels are not altered in disease-associated brain regions of APPSL and APPSL/PS1M146L mouse models of Alzheimer's disease: relationship with the lack of neurodegeneration? **Int J Alzheimers Dis**, 2010 Dec 27.

3. Martin L, Latypova X, Terro F. Post-translational modifications of tau protein: implications for Alzheimer's disease. **Neurochem Int** 2011a; 58: 458-71.
4. Martin L, Page, G, Terro, F. Tau phosphorylation and neuronal apoptosis induced by the blockade of PP2A preferentially involve GSK3beta. **Neurochem Int** 2011c (minor revision); M/S number NCI-D-11-0001.
5. Martin L, Magnaudeix A, Wilson, C, Yardin, C, Terro F. The new indirubin derivatives inhibitors of GSK3, 6-BIDECO and 6-BIMYEO, prevent tau phosphorylation and apoptosis induced by the inhibition of PP2A by okadaic acid in cultured neurons. **J Neurosci Res** 2011b (minor revision) 2011; M/S number jnr-2011-jan-4076.
6. Couturier J, Paccalin M, Morel M, Terro F, Milin S, Pontcharraud R, Fauconneau B, Page G. Prevention of the β-amyloid peptide-induced inflammatory process by the inhibition of double-stranded RNA-dependent protein kinase in primary murine mixed co-cultures. **NBA** *under review*.

Team III: Neurobiology and Neuropharmacology of Addiction

We are grateful to the AERES committee for the general appreciation of our past research activity and future projects.

We agree with the comment of the committee that the project, as presented in the manuscript, may be currently too ambitious to be performed entirely with the present funding and personnel. However, in 2011, we are going to submit several grant proposals (including 2 ANR as Principal investigator) that may allow us recruiting one or two post-docs and perform our research projects. In addition, we are actively searching for young scientists with excellent CVs and technical/scientific skills complementary to those present in the lab, to apply for researcher positions (CNRS/Inserm) and join our team. Furthermore, we have set up important national and international collaborations that will allow performing key experiments using approaches complementary to ours. Finally, we hope through our patent and interactions with CROs to be able to obtain funding from the pharmaceutical industry.

If our projects will not receive major funding, we will focus our efforts on projects that are most advanced and for which we expect to gain most visibility. As noted, by the AERES committee we have already shown our ability to maximize our scientific output even with limited resources.

Since the AERES visit, three manuscripts from our team have been accepted for publication in international peer-reviewed journals.

1. Thiriet N, Agasse F, Nicoleau C, Guégan C, Vallette F, Cadet JL, Jaber M, Malva JO and Coronas V. *NPY promotes chemokinesis and neurogenesis in the rat subventricular zone*. **J Neurochem** (2011) in press
2. El Rawas R, Thiriet N, Lardeux V, Jaber M, Solinas M. *Early exposure to environmental enrichment alters the expression of genes of the endocannabinoid syste*m. **Brain Research** (2011) in press
3. Chauvet C, Lardeux, Jaber M, Solinas M. *Brain regions associated with the reversal of cocaine conditioned place preference by environmental enrichment* **Neuroscience**. In Press

Team IV: Psychobiology of Compulsive Disorders

We are grateful to the AERES committee for his overall analysis and appreciation of our research project. We would like to address some specific points:

Weaknesses and threats

1. • *Limited management experience*: We have already trained several post-doctoral fellows and PhD students in new techniques and we have also supervised post-doctoral research projects as attested by last-author publications recently accepted. We are currently preparing three original manuscripts, which experiments have been performed by our Poitiers team. Additionally, the PI has recently entered the editorial board of an open access journal (Brain and Behaviour) supporting his abilities to manage international editorial responsibilities.

2. • *Limited size of the team:* In January 2011 we have recruited a post-doctoral fellow whose expertise in the field of obsessive compulsive disorders will help the consolidation of our translational research projects. We have supported the presentation of two candidates to the CNRS/INSERM researcher recruitment program this year, but who unfortunately have not yet been successful (they still have to pass the CNRS 27 section shortly). We have also written new grant applications that will hopefully allow us to recruit them as post-doctoral fellows if they do not obtain a researcher position this year.

3. • *Lack of private funding:* Since January 2011 we have established relationships with pharmaceutical companies. Thus, we are currently performing experiments for a contract with AB sciences and are discussing with a major pharmaceutical company for a broader project. In addition, we have obtained new funding from IREB and Gilles de la Tourette foundation.

Recommendations

4. *Validate the confidence put by publishing shortly "Poitiers-derived" studies:* Since October 2010 we have had six publications among which three are "Poitiers-derived" (publication 1, 5, 6):

    1. **2011:** Murray J, Everitt BJ, **Belin D.** *N-Acetylcysteine reduces early and late-stage cocaine seeking without affecting cocaine taking in rats,* **Addiction Biology.** In Press. (IF: 4.73)

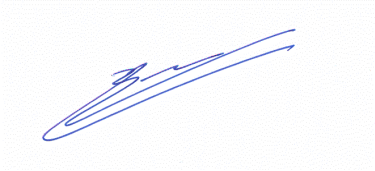
2. **2011:** Molander A, Mar A, Norbury A, Steventon M, Moreno-Montoya M, Caprioli D, Theobald DEH, **Belin D**, Everitt BJ, Robbins TW, Dalley JW. *High impulsivity predicting vulnerability to cocaine addiction in rats: Some relationship with novelty preference but not novelty reactivity, anxiety or stress*. **Psychopharmacology**, in press (IF: 4,182)
3. **2011: Belin D**, Berson N, Balado E, PV Piazza, V Deroche-Gamonet. *High novelty preference rats are predisposed to compulsive cocaine self- administration,* **Neuropsychopharmacolgy***, 36: 569-579* (IF: 6, 716)
4. **2011:** Badiani A, **Belin D**, Eipstein D, Calu D & Shaham Y. **Heroin and cocaine *addictions*: do the differences matter? Nat. Rev. Neurosci.** Invited review, submitted (IF: 26.485)
5. **2011: Jaafari N**, Rachid F, Rotge JY, Polosan M, El-Hage W, **Belin D**, Vibert N, Pelissolo A. *Safety and Efficacy of Repetitive Transcranial Magnetic Stimulation in the Treatment of Obsessive-Compulsive Disorder: A Review*. **World Biological Psychiatry** (IF: 5.564)
6. **2011: Belin D**, Daniel ML, Lacoste J, Belin-Rauscent A, Bacconnier M, **Jaafari N**. *Insight: perspectives étiologiques et phénoménologiques dans la psychopathologie des désordres obsessionnels compulsifs.* **Annales médico-psychologiques**. In Press (IF: 0.857)

Mohamed Jaber
LNEC Project Director

The University of Poitiers joins to all the observations made by the LNEC Project Director.

Poitiers on April 14th, 2011

The Vice-president in charge of the Research



Professor Olivier Bonneau

Laboratoire de Neurosciences Expérimentales et Cliniques
LNEC- M Jaber

Comments, answers and additional information to the AERES evaluation report

General comments

1. Local context: short reminder

- The main aim of this new research unit is to put together all teams working in the field of Neurosciences in Poitiers. This interdisciplinary project brings together researchers from different conceptual backgrounds (psychobiologists, cell and molecular biologists, toxicologists, electrophysiologists, neuroanatomists, neuropharmacologists, clinicians, …) to provide better understanding and, potentially, new therapeutic approaches to neurodegenerative diseases, addiction and compulsive disorders.

- Four sets of topics have emerged that federate all the research activity in Neurosciences in Poitiers around which four teams were constituted. The structure of the LNEC will be organized in teams largely autonomous, although not isolated, both scientifically and financially. Cross-talk and synergy between teams will be encouraged through, for instance, a priority for PhD fellowships for common projects.

- The LNEC project will be a part of a SFR project (Federative Structure of Research) with the aim of federating all Biology-Health laboratories around common scientific aims (cancer research, canalopathy, pharmacology and neurosciences) and technical facilities. This new SFR should also help increase the visibility of research performed in Poitiers at the local, national and international levels with calls for post-doctoral fellowships and subsequent funding to help install new teams. We will also be a part of a thematic SFR project in Neurosciences at Tours, which will give us access to imaging facilities.

- Poitiers and Tours CHUs (Hospital-University Center) have very close clinical connections. The Neurosciences clinical and pre-clinical activities have been identified as the major elements between these two centers and are considered priorities for future development. Both CHUs have specific grant calls to encourage collaborations between the two centers, and our group has recently received related funding.

2. *Relation with the private sector:* we have several ongoing contracts and collaborations.
    a. Team 1: BIOALTERNATIVES (Gençay-FRANCE) (2009) “In vitro pharmacological tests for the toxicity/safety of various compounds on primary dopamine neurons”
    b. Team 2: BIOALTERNATIVES (2009), ”The role of astrocytes in the physiopathology of Alzheimer's disease”. Furthermore, the team leader has submitted an ANR MALZ 2011 project with the Bio*alternatives* company as a partner.
    c. Team 3: The team leader is a scientific consultant for the CRO Porsolt Inc.
    d. Team 4: AB Sciences (2011) Identification of potential therapeutic effect of XX on stimulant and opiate addictions: preclinical analysis in the rat. We are also in advanced discussion with a major international pharmaceutical company for a preclinical contract aimed at identifying the potential addictive properties of a phase II molecule.
    e. The Deputy director has recently obtained a major contract (2,4 M€) with ABBOTT pharmaceuticals as he is leading a multicentric investigational trial in the Parkinson’s disease domain.

LNEC-University of Poitiers Building B36, 1 rue Georges Bonnet-BP 633, 86022 POITIERS cedex – FRANCE. tel.: 33 (0) 5 49 45 39 85 fax: 33 (0) 5 49 45 40 14. Email: Mohamed.jaber@univ-poitiers.fr

3. *Heavy teaching load, lack of significant number of technical and administrative staff:* we agree with the committee who raised these important points. We hope that when the new laboratory will be labelled, the local and national institution will significantly increase their support. The university has already agreed to allocate a financial manager and a research engineer to the Unit.

4. *Increase PhD student number:* the last three years, every year, 2 PhD fellowships from the French Minister of Research have been allocated to LNEC members. Although we do agree that the number of PhD students should increase, the local doctoral school has been supporting the creation of this new research unit significantly.

5. *The operational capability of team 2:* In the last 5 years, team 2 has had very intensive and fruitful interactions with clinical scientists as attested by:
    a. Several publications in the last 5 years in journals such as JBC, JCMM, JAD, J. Neurochem and NBD. The implication of clinicians in these papers is significant as attested by their signature in first or last position.
    b. Many clinicians from the local hospital have received and receive training in preclinical neurosciences by members of team 2.
    c. Members of this team have been key in putting together and running the CPER project 'aging and handicap" that is led by The Unit director.
    d. In the last 5 years, team 2 have raised 636 000 euros (LECMA, AIRMA, PHRC CYTOCOGMA, AAP PRES Limousin-Poitou-Charentes, ACI Tours-Poitiers, AAP Biology Health of CHU and Faculty of Medicine and Pharmacy) in addition to three PhD fellowships for young researchers (180 000 euros).
    e. A PU-PH, within this team, is the PI of a national and multicentric PHRC including a translational axis with the head of team 2.

6. *Balance funding between the teams:* since the AERES visit the management board has been regularly meeting. It is composed of the General Director, Deputy Director and the heads of research teams. Management regulations have already been set and voted for. Among the decisions that have been made, the management board agreed that whenever possible, 10-20% of grant allocations (depending on the type of the grant) and recurrent funding will be withheld by the general director and would be allocated to designated research projects.

Team I: Cell Therapies in Brain Diseases

We would like to thank the committee for its positive evaluation and suggestions. Overall, we are in agreement with the present report and therefore have a limited number of comments.

1. « T*he control of cell fusion and teratoma formation following transplantation of mouse-ESC-derived neural progenitors. This debate is behind us and a consensus has definitely been reached on the necessity to acquire a post-mitotic stage of differentiation before transplantation »*.

We do agree that the risk of teratoma formation may be reduced by prolonged cell differentiation before its engraftment. However, pre-differentiated ESCs or ESC-derived precursor cells might still form teratoma after transplantation into animals as previously reported. From the safety standpoint, and since these are the types of cells that we will be using, we believe that the tumorigenic ability of ESCs should be controlled.

2. *« Potential of ESC therapy in a rat model of Parkinson's disease. This aim is the most fragile of the three since a number of top international groups compete in the field. However, one of the orientations taken by the Team, the exploration of axonal guidance molecules, remains original and less furiously investigated by others. Inclusion of in vivo imaging in the set of techniques used by the team is quite relevant".*

We agree that this is a very competitive field. However we have an international solid

reputation in the field of cell therapy in Parkinson's disease as attested by:

(i) The originality of our approach which is based on cell transplantation within the lesioned site, the substantia nigra and not within the target site, the striatum as widely performed currently.

(ii) Our recent invited review in Trends in Neuroscience with the exclusive *Cover* illustration (issue of March 2011).

(iii) The recent acceptance of a FENS Forum 2012 symposium that we proposed in which the team leader is a speaker among three other world renewed speakers in the field of Parkinson's Disease (A Bjorklund, O Isacsson and S Dunnett). The symposium is entitled "Circuitry repair in Parkinson's disease: are we there yet?" and is chaired by the Unit Director.

Team II: Molecular Targets and Therapeutic in Alzheimer's disease

1. *The Team is in the process of reorganization inside the new unit with several former members joining other teams.*

The former members who joined other teams did so because of scientific coherence. They were working on aspects related to Parkinson's disease or Neuropharmacology which fits better with the projects of team 1 and 3 respectively. Two additional researchers will be joining this team by January 2012 among which a young and talented MCU-PH from Limoges working on autophagy in Alzheimer's disease.

2. *The team is also involved in … a locally coordinated PHRC running until 2012 to study the relation between peripheral cytokines and chemokines and cognitive decline in AD patients (66 k€/year).*

As a matter of fact, a PU-PH member of this team is the PI of this national and multicentric PHRC.

3. *The group is funded for the next two years and in the process of reorganization towards the work that they want to do.*

Our research team (previous EA) has a strong translational research activity through the presence of clinicians, pharmacists and scientists. In preparation for the future contract, this team has been restructuring for the last two years at the level of scientific projects, grants and researchers.

4. *There is a wide range of success to grant applications from rather impressive (team 4) to very good (team 1) and average (teams 2, 3)." and "Insufficient funding in two of the four teams".*

Between 2006 and 2010, the GREVIC/team 2 received 636 000 euros in funding: LECMA, AIRMA, PHRC CYTOCOGMA, AAP PRES Limousin-Poitou-Charentes, ACI Tours-Poitiers, AAP Biology Health of CHU and Faculty of Medicine and Pharmacy. In addition, this team has benefited from three PhD fellowships (180 000 euros).

5. *There is definitively a very high and clever-thought innovative research in 3 out of the 4 teams of the unit." "Three of the four teams develop original and innovative research in their respective fields".*

Team 2 has a national and international scientific specificity, which is the work on peripheral blood cells of patients with Alzheimer's disease. Exploring the involvement of these cells in the physiopathology of AD is original and innovative, and to our knowledge not investigated by other groups in France. It was a deliberate choice not to detail this project in the AERES document; nevertheless, it has been developed in the project ANR MALZ filed last march with an industrial partner. However, we do recognize that the aims of this project focused on chemotaxis between the periphery and the CNS were not detailed in the document; this was mainly due to lack of space. Nevertheless, these goals are clearly developed in the project ANR MALZ filed last March with an industrial partner (*Bioalternative*-FRANCE). In addition, the evaluation committee has verbally raised the need to strengthen our team with an immunologist. Currently, we are in

discussion for a possible integration of two immunologists (MCU-PH and PU-PH) by September 2012.

List of Publications of team 2 since the AERES visit:

1. Noël A, Barrier L, Rinaldi F, Hubert C, Fauconneau B, Ingrand S. Lithium chloride and staurosporine potentiate the accumulation of pGSK3βTyr216 resulting in GSK3β activation in SH-SY5Y human neuroblastoma cell lines. **J Neurosci Res**, 2011 May;89(5):755-63.
2. Barrier L, Fauconneau B, Noël A, Ingrand S. Ceramide and related-sphingolipid levels are not altered in disease-associated brain regions of APPSL and APPSL/PS1M146L mouse models of Alzheimer's disease : relationship with the lack of neurodegeneration ? **Int J Alzheimers Dis**, 2010 Dec 27.
3. Martin L, Latypova X, Terro F. Post-translational modifications of tau protein: implications for Alzheimer's disease. **Neurochem Int** 2011a; 58: 458-71.
4. Martin L, Page, G., Terro, F.,. Tau phosphorylation and neuronal apoptosis induced by the blockade of PP2A preferentially involve GSK3beta. **Neurochem Int** 2011c (minor revision); M/S number NCI-D-11-0001.
5. Martin L, Magnaudeix, A., Wilson, C., Yardin, C., Terro, F.,. The new indirubin derivatives inhibitors of GSK3, 6-BIDECO and 6-BIMYEO, prevent tau phosphorylation and apoptosis induced by the inhibition of PP2A by okadaic acid in cultured neurons. **J Neurosci Res** 2011b (minor revision) 2011; M/S number jnr-2011-jan-4076.
6. Couturier J., Paccalin M., Morel M., Terro F., Milin S., Pontcharraud R., Fauconneau B., Page G. Prevention of the β-amyloid peptide-induced inflammatory process by the inhibition of double-stranded RNA-dependent protein kinase in primary murine mixed co-cultures. **NBA** *under review*.

Team III: Neurobiology and Neuropharmacology of Addiction

We are grateful to the AERES committee for the general appreciation of our past research activity and future projects.

We agree with the comment of the committee that the project, as presented in the manuscript, may be currently too ambitious to be performed entirely with the present funding and personnel. However, in 2011, we are going to submit several grant proposals (including 2 ANR as Principal investigator) that may allow us recruiting one or two post-docs and perform our research projects. In addition, we are actively searching for young scientists with excellent CVs and technical/scientific skills complementary to those present in the lab, to apply for researcher positions (CNRS/Inserm) and join our team. Furthermore, we have set up important national and international collaborations that will allow performing key experiments using approaches complementary to ours. Finally, we hope through our patent and interactions with CROs to be able to obtain funding from the pharmaceutical industry.

If our projects will not receive major funding, we will focus our efforts on projects that are most advanced and for which we expect to gain most visibility. As noted, by the AERES committee we have already shown our ability to maximize our scientific output even with limited resources.

Since the AERES visit, three manuscripts from our team have been accepted for publication in international peer-reviewed journals.

1. Thiriet N, Agasse F, Nicoleau C, Guégan C, Vallette F, Cadet JL, Jaber M, Malva JO and Coronas V. *NPY promotes chemokinesis and neurogenesis in the rat subventricular zone*. **J Neurochem** (2011) in press
2. El Rawas R; Thiriet N; Lardeux V; Jaber M; Solinas M. *Early exposure to environmental enrichment alters the expression of genes of the endocannabinoid syste*m. **Brain Research** (2011) in press
3. Chauvet C, Lardeux, Jaber M, Solinas M *Brain regions associated with the reversal of cocaine conditioned place preference by environmental enrichment* **Neuroscience**. In Press

Team IV: Psychobiology of Compulsive Disorders

We are grateful to the AERES committee for his overall analysis and appreciation of our research project. We would like to address some specific points:

Weaknesses and threats

1. • *Limited management experience*: We have already trained several post-doctoral fellows and PhD students in new techniques and we have also supervised post-doctoral research projects as attested by last-author publications recently accepted. We are currently preparing three original manuscripts, which experiments have been performed by our Poitiers team. Additionally, the PI has recently entered the editorial board of an open access journal (Brain and Behaviour) supporting his abilities to manage international editorial responsibilities.
2. • *Limited size of the team:* In January 2011 we have recruited a post-doctoral fellow whose expertise in the field of obsessive compulsive disorders will help the consolidation of our translational research projects. We have supported the presentation of two candidates to the CNRS/INSERM researcher recruitment program this year, but who unfortunately have not yet been successful (they still have to pass the CNRS 27 section shortly). We have also written new grant applications that will hopefully allow us to recruit them as post-doctoral fellows if they do not obtain a researcher position this year.
3. • *Lack of private funding:* Since January 2011 we have established relationships with pharmaceutical companies. Thus, we are currently performing experiments for a contract with AB sciences and are discussing with a major pharmaceutical company for a broader project. In addition, we have obtained funding from IREB and Gilles de la Tourette foundation.

Recommendations

4. *Validate the confidence put by publishing shortly "Poitiers-derived" studies:* Since October 2010 we have had six publications among which three are "Poitiers-derived" (publication 1, 5, 6):
    1. **2011:** Murray J., Everitt BJ., **Belin D.** *N-Acetylcysteine reduces early and late-stage cocaine seeking without affecting cocaine taking in rats,* **Addiction Biology.** In Press. (IF: 4.73)
    2. **2011:** Molander A, Mar A, Norbury A, Steventon M, Moreno-Montoya M, Caprioli D, Theobald DEH, **Belin D**, Everitt BJ, Robbins TW, Dalley JW: *High impulsivity predicting vulnerability to cocaine addiction in rats: Some relationship with novelty preference but not novelty reactivity, anxiety or stress.* **Psychopharmacology**, in press (IF: 4,182)
    3. **2011: Belin D.**, Berson N., Balado, E., P.V. Piazza, V. Deroche-Gamonet: *High novelty preference rats are predisposed to compulsive cocaine self- administration,* **Neuropsychopharmacolgy**, *36:569-579* (IF: 6,716)
    4. **2011:** Badiani A., **Belin D.**, Eipstein D., Calu D. & Shaham Y. **Heroin and cocaine *addictions*: do the differences matter? Nat.Rev.Neurosci.** Invited review, submitted (IF: 26.485).
    5. **2011: Jaafari N.**, Rachid F., Rotge JY.,Polosan M., El-Hage W., **Belin D.**, Vibert N., Pelissolo A., *Safety and Efficacy of Repetitive Transcranial Magnetic Stimulation in the Treatment of Obsessive-Compulsive Disorder: A Review.* **World Biological Psychiatry** (IF: 5.564)
    6. **2011: Belin D.***, Daniel ML*., Lacoste J.,Belin-Rauscent A., Bacconnier M., **Jaafari N**. *Insight: perspectives étiologiques et phénoménologiques dans la psychopathologie des désordres obsessionnels compulsifs.* **Annales médico-psychologiques**. In Press (IF: 0.857)

Poitiers the 14th of April 2011
Mohamed JABER
Head of the LNEC projet