Institut des maladies émergentes et des thérapies innovantes

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Institute of Emerging Diseases and Innovative Therapies

From the

CEA

May 2010

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

Section des Unités de recherche

AERES report on the research unit

Institute of Emerging Diseases and Innovative Therapies

From the

CEA

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

May 2010

Research Unit

Name of the research unit: Institute of Emerging Diseases and Innovative Therapies

Requested label: CEA Institute

N° in the case of renewal

Name of the director: M. Philippe LEBOULCH

Members of the review committee

Committee chairman

M. Roberto CHIESA, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy

Other committee members

Mrs Laure COULOMBEL, Inserm U 935, Paris, France

M. Hans KRETZSCHMAR, University of Munich, Munich, Germany

M. Thierry BARON, AFSSA, Lyon

M. Fabrizio TAGLIAVIANI, Fondazione IRCCS - Istituto Neurologico Nazionale Carlo Besta, Milan, Italy

Committee members suggested by CNU, CoNRS, CSS INSERM, CSS INRA, INRIA, IRD

Observers

AERES scientific advisor

M. Nicolas GLAICHENHAUS

University, School and Research Organization representatives

Mrs Anne FLÜRRY-HERARD, CEA

M. Gilles BLOCH, CEA

Report

1 • Introduction

- Date and execution of the visit

The site visit started on February 23 at 2:00 pm and ended at 2:00 pm on February 24, 2010.

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

The Institute of Emerging Diseases and Innovative Therapies (iMETI) is located within the CEA's Fontenay-aux-Roses campus, near Paris. It was created in 2007 and includes the Division of Prion Disorders and Related Infectious Agents (SEPIA), the Division of Immunology (SIV), and the Division of Innovative Therapies (STI). The field of research of iMETI is the pathophysiology of human diseases with a focus on developing drugs, vaccines, gene and cell therapies, and diagnostic and decontamination procedures for unconventional infections. The institute is involved in many national and international collaborations with academic institutions and private biotechnology companies. The iMETI has been awarded a number of research grants from national and international funding agencies, including the European Community and the US National Institute of Health (NIH).

- Management team

The head of the Institute is M. Philippe Leboulch, who is also the director of the Division of Innovative Therapies (STI), and visiting professor at Harvard University, USA. M. Roger Le Grand is head of the Division of Immunology (SIV), and M. Jean-Philippe Deslys coordinates the Division of Prion Disorders and Related Infectious Agents (SEPIA).

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	18	19
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	12	ND
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	28	27
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	18	18
N6: Number of Ph.D. students (Form 2.7 of the application file)	6	7
N7: Number of staff members with a HDR or a similar grade	6	7

2 • Overall appreciation on the research unit

• Summary

The iMETI activities focus on diagnosis, prevention and therapy of human diseases. The Unit benefits from internationally recognized experts in the field of immunology, unconventional infectious diseases, and gene and cell therapy, who have developed competitive research programs. The iMETI has state-of-the-art technologies and biosafety level 3 (BL3) animal facilities for preclinical studies in rodents and non-human primates, and is involved in important collaborations with national and international partners. The projects span studies of viral/host interactions using primate models of human infections, gene therapy and control of cell expansion, and investigation of the pathophysiology of prion and related disorders. Recent research at iMETI has led to a number of important publications in high-profile journals, including Science, PloS Biology, Molecular Cell, Cell Stem Cell, Journal of Clinical Investigation and Lancet. Research at iMETI was instrumental for developing a diagnostic test for bovine spongiform encephalopathy (BSE) which is now used worldwide, and led to the first clinical trial of lentiviral gene therapy for thalassemia and sickle cell disease, adrenoleukodystrophy, as well as to the discovery of a new molecule for chronic myeloid leukemia which is currently under phase II clinical trial.

• Strenghts and opportunities

- Diversity of programs covering hematology, immunology, infectious diseases with a good balance between basic and translational approaches

- State-of-the-art facilities and platforms rarely available within the same center, including animal facility for non-human primates, production of viral vectors and cytometry. Platforms for genetic and proteomic screening, and in vivo imaging are also available through collaborations, and HTS platform for microarray tagging is under development.

- Excellent BL3 laboratories and animal facilities. iMETI is one of the few reserch institutes worldwide with a BL3 facility for studies in non-human primates, which is available for collaborative research projects with academic and industrial partners within and outside France.

- Strong collaborations with academic and industrial partners, and international programs.

- The research projects of the three divisions cover very relevant fields of biomedical research, namely modeling of human diseases in non-human primates, recombinant vaccine development, pathophysiology of non-conventional infectious agents, comprehensive development of new gene and cell therapies, particularly in congenital hemoglobin disorders, leading to clinical trials.

- The institute has an excellent publication record.

- There are opportunities for training of Ph.D. students and exchange with physicians to develop research projects involving studies in animal models. The immunology (SIV) and gene therapy (STI) divisions have a very dynamic recruitment policy (3 senior scientists and 9 post-doc recruited in 2009).

• Weaknesses and threats

- Logistic problems were pointed out by the director of the Unit, M. Philippe Leboulch, concerning the inconvenient location of part of the animal facility and SIV laboratories.

- There seems to be poor scientific interaction between the three divisions, but the creation of the Institute is recent, and for closer interactions to develop, decision should be made to relocate the SIV group on the CEA campus close to the other two groups.

- The distribution of the personnel (principal investigators, post-docs, technicians and students) is very different between the three divisions. SEPIA has many technicians but only two senior scientists and one post-doc who has joined the group very recently.

- Recommendations to the head of the research unit

The SIV and STI divisions of the iMETI were evaluated by AERES at the end of 2008, scoring A and A+, respectively. Since then corrective actions have been undertaken following the AERES recomendations and there have been notable scientific achievements; therefore, no specific comments are offered by this committee on the activities of these divisions. The following recommendations pertain mainly to SEPIA. The topic of SEPIA research is timely, important and appropriate, and the enterprise is growing at healthy rate. Dr. Deslys is to be congratulated, and should continue in his endeavours to create a new and vibrant axis of research on prion diseases in Fontenay-aux-Roses. It was noted, however, that SEPIA's research program spans a number of different areas, some addressing reasonable issues but not necessarily presented as being organized around a main, long-term theme. Ideally a core theme would encompass a profound issue in prion and related disorders research, exhibit a continuity with previous activites, and project well into the future. In the last years the SEPIA division has developed unique models of sub-clinical and atypical prion diseases, which should be fully exploited for in-depth analysis of the pathophysiology. The head of the research unit should stimulate M. Deslys to steer his projects in a sharper way to achieve this goal, and to hire more experienced researchers at the PI and post-doctoral levels. It is also advisable to foster further collaborations between the three divisions.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	1
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	17
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	100%
A4: Number of HDR granted during the past 4 years	1
A5: Number of PhD granted during the past 4 years	7

3 • Specific comments on the IMETI

- Appreciation on the results

The overall productivity of the iMETI has been excellent. The Unit contributed significant advances in viral/host interactions, gene therapy and control of cell expansion, modeling of prion diseases in primates and developing decontamination procedures for prions. The researchers in the Unit are competitive at the highest international level in their fields, as can be assessed by a large number of publications in high-profile journals in the last four years. Seven Ph.D. affiliated to various universities (Paris VI, VII, XI) have been defended during the past four years. The Unit has developed numerous partnerships with industries and spin-offs, coordinated the European Network of Excellence Neuroprion and hosted the BioSecure Alliance Foundation, which funds research on prion decontamination and pathogenesis.

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

The members of the Unit have been invited to many conferences as guest lecturers and symposia. Since the last AERES evaluation the Unit has managed to recruit one security engineer for the whole institute, two senior scientists, four post-docs and eight students for the SIV division, one research scientist, two post-docs, ten students and one part-time secretary for the STI division, and one zootechnician and one laboratory aid for STI and SEPIA (split at 50 % of their time between the two divisions).

The SEPIA division of iMETI has coordinated the European Network of Excellence NeuroPrion, the biggest international network of prion researchers, which includes 52 partners from 20 different countries. The NeuroPrion has been extremely successful in promoting collaborations between different laboratories within and outside the EU, resulting in more that 350 publications on peer-reviewed journals. The NeuroPrion network has organized six international conferences on prion diseases (with an average of 700 attendees), and created a database of prion litterature and conference videos which are available to all NeuroPrion members.

The Unit has been very successful in raising funds from different sources, including the European Community, NIH, INSERM, PHRC and through contracts with biotech companies. Moreover, royalties from the BSE test developed at iMETI and commercialized by Bio-Rad have provided a significant income for CEA (approximately 55 millions of Euros), which was used in (small) part to subsidize the Unit.

- Appreciation on the strategy, management and life of the research unit

The iMETI is mainly focused on the prevention and cure of human diseases, such as HIV and prion infections, beta-hemoglobinopathies and chronic myeloid leukemia, and makes use of different approaches to address these issues including hosting biotech companies on site which are necessary for implementing the therapy trials. The creation of an institute with expertise in immunology, gene and cell therapies and atypical infections seems an excellent strategy. The director of the institute is well suited to lead this program. A closer interaction of the three Divisions seems desiderable and should be advantageous to all of them.

The Unit hosts internationals speakers, visiting scientists and internal seminars (unit meetings, project leader meetings and journal clubs). The personnel, including technicians, appears to feel well integrated in the scientific activities of the Unit, with possibilities to partecipate in scientific meetings.

- Appreciation on the project

There is an excellent collection of cutting-edge research projects ranging from studies on hematopoietic gene therapy, to HIV infections, mechanisms governing the balance between cell proliferation and differentiation, mechanisms of vaccine-induced immune response, viral/host interactions, and studies of atypical prion infections and decontamination procedures. The SIV and STI divisions seem to be on the right track to satisfactorily address all the questions raised during the last AERES evaluation in 2008. A detailed assessment of the SEPIA research program, which had not been assessed before, is offered in section 4 of this report.

4 • Appreciation team by team

Title of the team: SEPIA's unit

Team leader: M. Jean-Philippe DESLYS

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	2*
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)	17	17
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	16	16
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	1
N7: Number of staff members with a HDR or a similar grade	1	1

* One scientist is now full time in creation of a biotech company, and another one will be 64 years old next january 2011

- Appreciation on the results

In the last four years research at SEPIA has focused on developing models for assessing risk of transmission of BSE to humans and other species, and secondary transmission via blood transfusion or plasma derivatives. The group developed a prion model of BSE in cynomolgus macaque monkeys, which turned out very helpful to anticipate the risk of BSE transmission to humans. Recent experiments support the existence of silent carriers and atypical forms of prion disease in primates. Similar forms in humans could go undiagnosed, with clear implications for risk assessment and public health policies.

Since 2005 the main achievements were:

- Estimation of the risk of oral infection with the bovine spongiform encephalopathy agent in primates.
- Demonstration of prion infectivity in the blood of variant Creuztfeldt-Jakob disease (vCJD)-infected primates.
- Transmission of amyloidotic spongiform encephalopathy (BASE) to primates.
- Risk assessment of zoonotic potential of other animal prions, such as sheep scrapie, chronic wasting disease (CWD) of cervids, and protease-sensitive prionopathies of humans.
- Description of new "atypical" forms of prion disease in primates linked to low-dose exposure.
- Development of standardized procedures (the stainless steel wire method) for evaluation of prion contamination using both hamster and mouse prions, adopted as standard protocol for the "Agence française de sécurité sanitaire des aliment (AFSSA)" in 2009.

- Identification of efficient protocols for prion inactivation (first demonstration of efficiency of vaporized hydrogen peroxide).

- Development of alternative strategies for prion decontamination based on removal of prions from contaminated surfaces, followed by treatment with milder inactivating agents compatible with fragile devices (e.g. endoscopes).

- Development of procedure for reducing potential prion infectivity from meat and bone meal (MBM), large surfaces (e.g. MBM storage sites or trucks used for MBM transportation), and for depleting prions from blood.

- Creation of a blood bank of prion-infected sheep and primates for evaluation of blood tests.

- Preliminary evidence of a possible role of small ribonucleic acid molecules in prion infectivity.

- Use of "modulator" molecules to increase the efficacy (and reduce the side effects) of psychotropic drugs.

- Development of a web-based tool to favor exchange of information between scientists.

Since 2005 SEPIA has published 19 papers with an average impact factor (IF) of 4.5, including one paper in Lancet (IF 23.4). Among these papers, 5 were signed by a member of the team as last or first author : PlosOne (2008), Acta Neuropathol (2008), GMS Krankenhhyg Interdiszip (2008), J Gen Virol (2007), Lancet (2005)

Two PhD thesis have been produced, as well as communications to the governement agencies about prion risk assessment.

SEPIA coordinates and hosts the activity of the European Network of Excellence NeuroPrion (now NeuroPrion Association), which includes 52 partners from 20 different countries, and collaborates directly with a number of labs of the network. The SEPIA is also involved in numerous collaborations with biotech companies some of which are hosted at iMETI within the NeuroPrion platform and are co-funders of the Alliance Biosecure Foundation.

- 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 has been invited to several conferences as guest lecturer since 2006.

The NeuroPrion and Alliance Biosecure platforms have the potential for attracting scientists from other institutes. Two senior researchers from Italy and the USA respectively have spent sabbaticals at SEPIA, and 4 other scientists are expected in the next future.

The Unit has been very successful in raising funds and participating to industrial and public clusters.

- Appreciation on the strategy, management and life of the team

The strategy of SEPIA is oriented towards innovative research programs designed for use by public authorities. The Unit is a reference center for the cynomolgus macaque model of prion disease and is a source of reference blood samples. This favors the synergy and cooperation with research teams interested in the primate model, with European and French public health authorities for issues concerning prion biosafety, and with pharmaceutical industries for the evaluation and improvement of manifacturing processes (e.g. blood derivatives). Basic science research is somewhat weaker, but is planned for the future, and collaboration with other groups at iMETI should help developing cutting-edge projects.

The research activities of SEPIA are coordinated by the two SEPIA permanent researchers, who are in charge of the studies in primates. A senior research engineer, is in charge of identifying the needs of public and industrial partners and facilitating the technological transfer of research. Due to its strong involvement in applied research projects the Unit counts a large number of technicians, with few post-docs and students.

The international visibility and communication is very good due to the presence of the NeuroPrion platform and the intelligent use of web tools. The Unit has developed an innovative software, which could be used by Universities to develop an international virtual campus, as well as electronic tools for managing the budget and the experiments performed in the animal facilities (currently housing 110 primates and 12,000 rodents).

- Appreciation on the project

Ongoing projects include :

1) Risk assessment of low infectious of prions for human health in a primate model. Infection of macaques with low doses of prions induced accumulation of low levels of abnormal prion protein (PrPres) in lymphoid tissues and the animals developed clinical signs of disease after a long period (8-12 years post-inoculation). The blood of these animals was infectious despite very low or undetectable PrPres in lymphoid tissues, and the infected animals would have gone undiagnosed by tests currently performed in humans. In addition, the clinical, histopathological and biochemical patterns of these animals were very different from those typically observed. These analyses indicate that low exposure to prions may lead to atypical clinical patterns, different pathology and negative diagnostic tests. They also suggest that blood infectivity may be present in preclinical stages and may constitute a source of secondary contamination through transfusion and/or instrument contamination.

The project aims at identifying in the primate models the prion signature of silent and atypical diseases. It also aims at defining molecular signatures of emerging prion strains whose pathogenicity in humans is currently unknown, such as those arising from transmission of BASE, CWD, scrapie and protease-sensitive prionopathies.

The issue is very relevant and the experimental plan is clear. Animals at different times of incubation (from few months after infection to more than 10 years) will be subjected to neurological and behavioural analyses, and in vivo imaging. Several strategies for detecting abnormal PrP in the blood will be attempted, including an improved version of ultra-sensitive protein misfolding cyclic amplification (PMCA). The diagnostic potential of abnormal RNA sequences recently identified at SEPIA will be also tested.

2) Project Prion-Alzheimer. It is proposed to explore the molecular links between prion diseases and Alzheimer disease (AD), with a view to develop new therapeutical approaches. This projects is based on the observation that prion diseases and AD share a number of neuropathological and biochemical features, that PrP governs the beta-secretase cleavage of the amyloid precursor protein (APP), and binds amyloid-beta (A¤) oligomers, and that under certain experimental circumstances A¤ may propagate through a prion-like mechanism. Proposed studies include: i) biophysical analyses of PrP and A¤ polymerization and cross-seeding activity; ii) PMCA of pathological A¤ species for AD detection; iii) mapping of subcellular interaction and processing of APP and PrP in neurons; iv) breeding of APP/PS1 (and Tau) transgenic mice with mice expressing different levels of PrP; v) development of antibodies against A¤ multimers and Tau.

Although this project is potentially interesting, the rationale is weak and the experimental plan unclear. In particular, the committee felt that the published experimental evidence in favour of an interaction between APP and PrP was too preliminary to make a judgement on a functional link. Developing a research plan on the basis of limited evidence is not advisable. Nonetheless, the general concept was seen in a positive light as one means to dig into common mechanisms of pathogenesis of protein misfolding disorders. It would be advisable to find strong collaborators in the AD area and/or hire a senior scientist with specific expertise on AD.

3) Prion decontamination. This project was developed to address a request of the Ministry of Agriculture (DGAL) to secure MBM production and decontaminate surfaces that come in contact with MBM, and to develop a standardized procedure to evaluate decontamination procedures. Undoubtedly, the Unit has the capability and necessary experimental tools and lab facilities to successfully develop this project.

4) Start-up Theranexus. This project stems from the serendipitous observation that certain molecules have a modulatory effect on the activity of differnt classes of psychoactive drugs. The « modulator » technology has been patented, and it will be proposed to pharmaceutical companies to evaluate its efficacy on different psychoactive drugs.

Other projects at SEPIA include the creation of infrastructures to support research:

5) Project ENCRE-Start-up WeCoNext (led by two engineers to be recruited). The aim of this project is to develop a virtual infrastructure based on an innovative high-speed web browser software for remote teaching and training of students, online scientific conferences, etc. This is an excellent idea and the iMETI/SEPIA has the necessary capabilities and technology to develop the project.

6) Project NeuroPrion. This projets aims at continuing the activity of the NeuroPrion Network that ended in December 2009. Towards this aim the NeuroPrion Association was created with the goal of organizing events and web activity for exchange of information between scientists in the prion field, and training of young researchers. Given the success of the NeuroPrion Network, the idea of continuing its activity is commendable and worth pursuing.

7) Project Foundation. This project aims at developing innovative technological strategies to face environmental problems with a strong potential impact on human health. This will be achieved through collaboration between CEA, INRA and INERIS aimed at collecting and delivering funding for research, and improve cooperation between different institutes to face emergent practical problems. This is also a commendable project.

- Conclusion :

  – Summary

The SEPIA Division of iMETI pursues both applied and basic research, with projects ranging from prion disease pathophysiology and decontamination procedures, studies on modulators of psychoactive drugs, development of innovative technological platforms and networking activity. The productivity in the last four years has been good. Applied research on prion decontamination has been very fruitful, and the Unit has developed unique experimental models of unconventional prion diseases in primates, which could provide important insight into the physiopathology of these diseases and the potential risks for human health. This issue is timely and very relevant, and the experimental approach is clear. There is also a commitment for new research projects on the relationship between prion and Alzheimer's disease, but the experimental plan seemed quite vague and the Unit lacks expertise in the AD field. The team should recruit expert scientists and/or find strong collaborators in this area.

  – Strengths and opportunities

- The Unit has an excellent expertise in applied research, and has developed strong and proficous collaborations with industries, something that eludes many research groups;

- The Unit has very good experience in networking activity (the team leader was the coordinator of an European Network of Excellence that was very successful);

- The Unit has established and has access to a unique animal facility in which monkeys could be infected with prions and followed for many years;

- The team has interesting data on silent carrier monkeys that could be potentially an important issue for human health (low doses of infectious agents);

- There is opportunity for collaboration with the other groups at iMETI. On this note, transversal research projects on lentiviral gene transfer of PrP mutants and prion propagation in iPS cells have been started in collaboration with the STI Division.

  – Weaknesses and threats

- The rationale and experimental plan of the project Prion-Alzheimer is not clear;

- The team has obtained preliminary data on the role of RNA as a cofactor for prion infectivity, but this needs to be confirmed to be developed into a real project;

- Two scientists have left the team, and SEPIA now includes only two senior scientists and one “habilitation à diriger les recherches (HDR)”.

– Recommendations

The team should state clearly how much effort it wants to devote to fundamental research. If a choice to do more basic research is made, the team should recruit more experienced senior scientists, for example in the field of amyloidosis or primate physiopathology, to reach this goal.

Note de l’unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l’environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	A	B	B

Direction des Sciences du Vivant

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Fontenay-aux-Roses, le 10 juillet 2010

Monsieur Pierre Glorieux
Directeur de la section des unités
AERES

Monsieur et Cher Collègue,

A la suite des évaluations précédentes de deux des trois services constituant notre institut (iMETI) par l'AERES, qui avait obtenues les notes de "A+" pour le Service des Thérapies Innovantes (STI - Chef de service: Philippe Leboulch) et de "A" pour le Service d'Immuno-Virologie (SIV - Chef de service: Roger Le Grand), nous avons reçu la visite d'un comité de visite international de l'AERES pour évaluer l'iMETI dans son ensemble ainsi que le dernier service restant à évaluer, le Service des Prions et Infections Apparentées (SEPIA - Chef de service: Jean-Philippe Deslys).

Je voudrais d'abord remercier les membres du comité de visite de l'AERES pour l'évaluation très favorable qu'ils ont bien voulu porter sur l'ensemble de l'iMETI.

L'iMETI prend également acte de la note de "B" attribuée par l'AERES pour l'évaluation du service SEPIA. Nous avons été extrêmement surpris par ce résultat qui ne correspondait pas aux commentaires qui avaient été faits lors de la visite du comité d'évaluation. Cette surprise est apparemment partagée par les experts eux-même d'après la lettre envoyée à l'AERES le 10 mai 2010 pour laquelle l'iMETI était en copie. Cette lettre du président du comité international d'experts choisi par l'AERES et signée par tous les experts indiquait notamment :

«We only recently had the opportunity to know the final evaluation of the iMETI/SEPIA Unit, which was given a very poor score (B for the Unit as a whole, …). This score is in sharp contrast with the overall positive judgment that was expressed by the Committee during discussion in Fontenay-aux-Roses, and that was written in the report submitted to AERES, the summary of which reads: … »

« In conclusion, we consider that the final evaluation of the iMETI/SEPIA Unit does not reflect the overall positive judgment given by the Committee. The reasons for this discrepancy are not clear, and raise the question of what is the purpose of having international independent experts evaluating French research Institutes if their judgment is not taken into account. »

Il est à noter que la principale critique du rapport était le manque de précisions sur l'un des 2 axes de recherche fondamentale, le futur axe prion-Alzheimer. Or, si ces précisions n'avaient pas été fournies, c'est parce qu'elles portaient sur un sujet stratégique en débat dans la communauté scientifique en raison des risques de conflits d'intérêt avec des compétiteurs potentiels et de la nécessité de protection de la propriété intellectuelle sur une

approche originale qui était en cours de soumission à l'ANR. Ces précisions étaient en fait apportées en grande partie dans le projet *« ADPrion - Relations moléculaires entre la maladie d'Alzheimer et les maladies à prions : une nouvelle voie dans la lutte contre les démences »* (porteur de projet Dr JP Deslys, IMETI/SEPIA) qui vient d'être accepté par l'ANR dans le cadre du programme *« Maladie d'Alzheimer et maladies apparentées – édition 2009 »* (programme trilatéral avec le Québec et les autres provinces du Canada). Ce projet, validé par les experts internationaux mandatés par l'ANR, fait désormais partie des 5 projets sélectionnés sur 50 projets soumis dans le cadre de ce programme. Par ailleurs le SEPIA vient de déposer un premier brevet sur le sujet et d'autres développements en cours doivent également faire l'objet de brevets et demeurent soumis aux mêmes règles de confidentialité.

L'autre axe de recherche fondamentale du SEPIA repose sur le modèle primate qu'il a développé et pour lequel son expertise unique est reconnue au niveau international : il explore les risques liés aux faibles doses de prions pour la santé humaine en général et la transfusion sanguine en particulier. Ces approches présentées en détail à l'AERES avaient été particulièrement appréciées par les experts et elles avaient fait l'objet de 2 projets soumis à l'ANR dont les résultats sont désormais connus:

- Le projet *« LowPrion – Evaluation de l'effet des faibles doses de prions pour la santé humaine dans un modèle expérimental de primate »* (porteur de projet Dr E Comoy, IMETI/SEPIA) a été accepté par l'ANR dans le cadre du Programme Blanc - édition 2010 (SVSE 3 : Microbiologie, immunologie, infectiosité).

- Le projet *« BLOODSECUR – Sécurisation des composés sanguins vis-à-vis de la transmission du prion lors des transfusions sanguines »* (porteur de projet C. Sumian, Sté MacoPharma dont l'équipe de R&D sur les prions est hébergée au SEPIA) a été accepté par l'ANR dans le cadre du Programme Biotechnologies – édition 2010.

Enfin, concernant la valorisation, les experts avaient trouvé très intéressant le projet de spin-off basé sur un brevet déposé en 2008 par le SEPIA. Désormais, ce projet porté par un chercheur du SEPIA vient d'être validé par OSEO après une expertise du cabinet Ernst & Young : il est l'un des projets du CEA primés au 12ème concours national d'aide à la création d'entreprises de technologies innovantes dans la catégorie émergence dont le prix vient d'être remis par la Ministre de l'Enseignement supérieur et de la Recherche. Pour mémoire, le délai entre le dépôt par un chercheur du SEPIA du brevet sous-tendant le test prion (1998) et sa commercialisation à partir de 2001 (avec à ce jour plus de 70 millions d'euros de retours pour le CEA) doit être considéré comme exceptionnellement court pour le système économique : la publication qui avait suivi (Deslys et al, Nature 2001) et avait contribué à sa reconnaissance internationale serait aujourd'hui nettement plus décalée dans le temps. Ainsi, concernant les autres travaux qui avaient été accomplis à la demande du Ministère sur la problématique de la décontamination des prions, la publication des résultats sera bien évidemment postérieure à leur protection intellectuelle prévue d'ici trois mois mais dépendra également des contraintes économiques pour permettre une valorisation optimale.

Au total, la notation "B" du SEPIA annoncée par l'AERES semble reposer sur des critères en profond décalage avec la valeur réelle du SEPIA, et ne correspond ni à l'opinion des experts qu'elle a elle-même sélectionnés ni à celles de trois instances indépendantes d'experts de l'ANR. Nous souscrivons totalement au souhait exprimé dans le rapport de l'AERES de renforcer l'équipe du SEPIA qui a développé une stratégie de développement originale et s'est donné les moyens scientifiques de faire face à la crise financière annoncée.

Je vous remercie de l'attention que vous voudrez bien porter à cette lettre, et je vous prie de croire, Monsieur et Cher Collègue, en ma sincère considération.

Philippe LEBOULCH

Inserm