IMRB - Institut Mondor de recherche biomédicale

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Mondor Institute for Biomedical Research

IMRB

Under the supervision of the following institutions and research bodies:

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

École Normale Supérieure

Centre National de la Recherche Scientifique - CNRS

Établissement Français du Sang

École Nationale Vétérinaire d'Alfort

Université Paris-Est Créteil Val de Marne - UPEC

January 2014

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

Department for the evaluation of research units

On behalf of AERES, pursuant to the Decree of 3 november 2006[1]*,*

- Mr. Didier HOUSSIN, president
- Mr. Pierre GLAUDES, head of the evaluation of research units department

On behalf of the expert committee,

- Mr Pascal BOUSQUET, chair of the committee

[1] The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n ° 2006-1334 of 3 November 2006, as amended).

Evaluation report

This report is the result of the evaluation by the expert committee, the composition of which is specified below.

The assessments contained herein are the expression of an independent and collegial deliberation of the committee.

Unit name:	Mondor Institute for Biomedical Research
Unit acronym:	IMRB
Label requested:	UMR_S
Present no.:	UMR_S 955
Name of Director (2012-2013):	Mr Georges GUELLAËN
Name of Project Leader (2014-2018):	Mr Jorge BOCZKOWSKI

Expert committee members

Chair:	Mr Pascal BOUSQUET, University of Strasbourg
Experts:	Ms Margarida AMARAL, University of Lisboa, Portugal
	Mr Derek J. BLAKE, University of Cardiff, United Kingdom
	Mr Patrice BOYER, University of Ottawa, Canada
	Mr Alan BURNS, University College of London, United Kingdom
	Mr Mario CLERICI, University of Milan, Italy
	Mr Jean-Francois DÉMONET, University of Lausanne, Switzerland
	Mr David ELAD, University of Tel Aviv, Israel
	Mr Krzysztof JAGLA, University of Clermont-Ferrand
	Mr Alain LE MOINE, University of Charleroi, Belgium
	Mr Massimo LEVRERO, University of La Sapienza, Roma, Italy
	Mr Antoine MAGNAN, University of Nantes (Representative of INSERM)
	Mr Juan NACHER, University of Valencia, Spain
	Mr Angelo PARINI, University of Toulouse
	Mr Miguel A PIRIS, University of Santander, Spain
	Mr Martin H. STEINBERG, University of Boston, United States

Scientific delegate representing the AERES:

Ms Sophie DE BENTZMANN

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

Mr Alain BERDEAUX (Representative of Doctoral School n°402)

Ms Lucie GOURNAY, UPEC

Ms Chantal LASSERRE, INSERM

Mr Benoît LESAFFRE, UPE

Ms Sharon PAPERKAMP, ENS

Mr Yves RÉMOND, CNRS

Mr Pierre TIBERGHIEN, EFS

Mr Renaud TISSIER, ENVA

1 • Introduction

History and geographical location of the unit

On January 1st, 2007, INSERM and the Université de Paris-Est Créteil (UPEC) created the "Institut Mondor de Recherche Biomédicale" (IMRB) as an emerging structure. 11 teams composed the IMRB. The aim was to gather different teams from the University Hospital and the Faculty of Medicine for improving interactions around common, optimized facilities, platforms and services. INSERM and UPEC labelled the IMRB with 14 teams for the 2009-2014 period. At that time, the IMRB was organized into 2 poles while in the present project, 3 departments are proposed.

In fact, at present teams taking part in the project are located at UPEC (Faculty of Medicine) (7 teams), Henri Mondor Hospital (7 teams), the Veterinarian School (Maison Alfort) (part of one team + animal facilities) and the French Blood Bank (EFS) (1 team). One group from Pierre et Marie Curie University is expected to join IMRB in 2016.

Management team

In its present form, IMRB is headed by Mr Georges GUELLAËN whereas the new project is defended by Mr Jorge BOCZKOWSKI who will be the next director. He will be assisted by a General Secretary and 3 committees (executive committee, supervisory board, scientific advisory board which includes 10 foreign experts).

AERES nomenclature

SVE1_LS4 Physiologie, physiopathologie, biologie systémique médicale

SVE1_LS6 Immunologie, microbiologie, virologie, parasitologie

SVE1_LS5 Neurobiologie

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	99	101
N2: Permanent researchers from Institutions and similar positions	21	32
N3: Other permanent staff (without research duties)	99	115
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	16	14
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	34	50
N6: Other contractual staff (without research duties)	53	56
TOTAL N1 to N6	**322**	**368**

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	66	
Theses defended	84	
Postdoctoral students having spent at least 12 months in the unit	34	
Number of Research Supervisor Qualifications (HDR) taken	25	
Qualified research supervisors (with an HDR) or similar positions	80	

2 • Assessment of the unit

Global assessment of the unit

Globally speaking, the teams of the IMRB have an excellent international reputation (117 international collaborations). IRMB itself is the clustering of 15 teams (growing to 18 for the next 5 years plus one which is expected to join the project next year). This gathering covers a wide range of different topics going from molecular psychiatry to cardiovascular diseases passing through genetics, nanotechnologies and molecular ecology. As a matter of fact, technological platforms, several facilities and patient cohorts constitute the common bond of the Institute. Over the past 5 years, the scientific production was excellent with numerous articles that appeared in either the best general journals such as N Engl J Med, Lancet, PNAS and others or in the mostly recognized journals in each speciality. The capability of the centre of accessing important funds from various local, regional, national and international sources is quite impressive (6.5 M euros/year, 9 "investissements d'avenir" grants, 9 European grants). Thanks to the organization as a plurithematic centre, the scientific and technological environment sounds very good. It greatly benefits from being close to various animal and clinical facilities and from being largely involved in different research training units such as doctoral schools in Ile de France region and master degrees in Créteil. As a consequence, the IMRB has proven to be capable of attracting all kinds of scientists: senior permanent researchers, postdoctoral fellows, PhDs and master students. In this line, one could just note a relative deficit in full time permanent researchers from national research institutions (INSERM, CNRS…).

Strengths and opportunities

- The scientific production is of very high quality.

- Most of the projects planned for the next 5 years are highly original and competitive.

- The IMRB has many translational projects.

- The science is very well integrated and linked with the university and the hospital (DHU).

- Fruitful relationships with the nearby veterinary school are effective.

- The IMRB has many relationships with industries (29 patent applications during the last 5 year period).

- The research has intense links with regional and national patient associations.

- Many actions toward facilitating scientific communication with the the media (TV, radio, newspapers) have been developed.

- The Centre has an excellent level of funding from various sources.

- The IMRB is sustained by solid technical and scientific environment.

- Good opportunities for advanced training (access to PhD and MSc students) have been noticed.

- The IMRB has developed excellent opportunities to integrate basic science with clinical research (Hospitals, Blood centre, Centre fo Clinical Investigation-CIC, etc,.).

- Well equipped core-facilities are available.

Weaknesses and threats

- A low rate of hiring new staff (namely international) has been noticed.

- The centre has an intermediate level of internationalization (staff, students).

- A heterogeneous level of contracts with industry among teams has to be mentioned.

- Regarding the size of the centre, there are few permanent full time scientists.

- Whereas most individual teams have confirmed international visibility and notoriety, this is not as evident for the centre itself.

- The staff complains about the lack of an efficient administrative and secretarial support.

- An effort should be made to quickly gather all the teams at the same place, with the exception of the Veterinary School and to distribute the spaces according to the real needs of the teams.

- The management of the centre is weak, or, for some aspects, non-existent in several domains such as, for instance, distribution of the budget and of the technical manpower across the teams or scheduling for scientific applications to ERC, INSERM.

- Although there are some, the remaining deficit of on-site (between teams and departments) interactions is a probable shortfall; some synergies and complementarities could be better exploited.

- The administrative integration of PhDs and PostDoctoral fellows as well as advanced courses to their intention are either insufficiently promoted or inexistent, respectively.

- Several platforms (bio-informatics, screening…) are still missing.

- A centralized press office that could quickly and effectively communicate scientific successes to the media is missing.

Recommendations

- The recruitment of young permanent scientists has to be increased, in particular, with international high-profile.

- The whole Institute has to promote its own international and national visibility.

- An effort has to be made to increase the added value of the centre through proper management organization: distribution of funds and manpower, organization of internal seminars, working out centre strategies for applications and recruitments.

- The integrated research can be stimulated (e.g., through inter-group collaborative projects, joint student supervisions, cycle of "fusion seminars", co-sponsored by 2 or more teams).

- The centre can further stimulate internationalization through a centre-scale plan (but also by a website in English).

- The centre can further stimulate contracts with industries for all groups through a centre-scale plan and organization of seminars with industries.

- Outreach and science & society activities (with high schools, public in general) can be further improved through overall IMRB outreach programs.

- The creation of a drug-discovery platform can be a leverage for more translational research.

- The future centre must take more advantage of the CIC.

- The future centre has to set up guidelines for using platforms.

- Various cycles of regular IMRB centre seminars have to be created.

- Some internal interactions between groups are already working but additional ones should be stimulated.

- In some domains, such as cardiology for instance, further stimulation of the involvement of clinicians in basic and/or translational research would be fruitful.

- The administrative resources of many teams need to be strengthened.

- The centre has to continue to develop high-throughput platforms.

- The future centre has to enhance teams' participation in EU projects.

3 • Detailed assessments

Assessment of scientific quality and outputs

Three different departments are proposed: 1/ Virus, Immunity, Cancer (VIC), 2/ Psychiatry, Neurology, Neuromuscular diseases (ESPRY), 3/ Aging, genetic and biomechanical aspects of cardiovascular and respiratory diseases, red-blood cell diseases and developmental diseases (PHYDES).

- VIC department (5 teams) focuses its research on HIV and HVC immunopathogenicity, oncogenesis, antiviral drugs, vaccines, immunopathology, organ transplantation; tumorogenesis in lymphoproliferative disorders, genito-urinary cancers.

- ESPRY department (5-6 teams, one group will be arriving in 2016) lines of research are development of gene and cell therapies in psychiatry, neurodegenerative disorders and neuromuscular diseases.

- PHYDES department (8 teams) in which various cardiac and respiratory diseases are investigated, including heart failure, myocardial ischemia, chronic obstructive pulmonary disease, pulmonary hypertension; genetic diseases such as cystic fibrosis, ciliopathies, neurocristopathies. New developments towards inflammation and senescence are in progress.

At present, the centre consists of 15 teams and a total of 322 staff members, being ~170 researchers.

Despite natural variations between teams, the staff numbers appear acceptable, but recruitment of only 14 researchers and 17 professors during the 2008-2013 period may appear insufficient since there was a net loss of 25 researchers during the same period. The 2015-2019 plan envisages new recruitments in increasing the team number to 18.

In the current evaluation period (2008-2013), the centre published 896 articles out of which 815 original articles and 81 reviews (~10/team/yr and 1.5 papers/researcher/yr). About 7% of this production was in journals with IF 10-15 and 3% in journals with IF >15. The centre has a record of 24 patents (0.3 patent/group/yr) and 91 completed PhD theses (~1 thesis group/yr and 0.1 thesis/ researcher/ yr) for the period.

Most of the research groups carry out high level research and have been very productive and with a significant proportion of publications in high profile journals. There is, however, considerable team heterogeneity. The number of PhD theses is acceptable, but its increase could be further stimulated, namely through PhD programs.

The centre and its 15 teams secured in 2008-2013 20 M€ + 9 M€ in "Investissements d'Avenir" for 10 yrs (2010-2020), i.e., 5.5 M€ + 1 M€/yr, or + 430 k€/team/yr, which is a comfortable funding level. The international funding as well as funding through 30 industry contracts is commendable (9 EU projects). There are plans for 2015-2019 to stimulate IMRB participation in EU projects and networks through a UPEC structure and through outsourcing. This should also be fostered through effective international collaborations, which could be initiated through an IMRB cycle of international seminars with invited lecturers.

Assessment of the unit's academic reputation and appeal

Most of the teams of the centre have a very good to excellent international reputation and apparently good international attractiveness. An overall IMRB internationalization plan should be adopted (including an english version of the website). All seminars should take place in English.

Several teams and team leaders take internationally leading roles in their domains: autism, HIV, HCV and others.

Most team leaders as well as many researchers are largely involved in national and international, mostly European (but not only) networks: as a non unique example, the leader of team 3 presides over a large international network on HIV and is also the head of an overseas French-American INSERM unit. A large number of them are actively involved in national (AERES and ANR in particular) and international evaluation tasks.

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

Although teams from the centre participated in several outreach initiatives, these appear to be mostly left to individual group initiative so far. IMRB should further stimulate outreach and science & society activities (with high schools, public in general) through overall IMRB outreach programs. Nevertheless, most of the teams have very active interactions with medical as well as public medias; several groups are also linked with patient associations.

Interactions with industry seem to be covered in the previous 5-yr plan but could be reinforced.

Assessment of the unit's organisation and life

The centre is headed by a director, assisted by a General Secretary and 3 committees. The directorial committee (comprising the General Secretary and 2 directors per pole) meets every 2 months to discuss scientific strategy, the distribution of funds and routine Centre issues. The Advisory Board (including 30 people with representatives of all personnel and teams) meets twice a year to be informed of the management decisions. The executive committee comprises the director, the General Secretary and team directors. Each department has its own council with all team leaders and representative of staff groups meeting monthly. This department organisation which parallels the Institute's organisation may appear somewhat redundant and heavy.

The governance to be implemented for the next 2015-2019 period appears reasonable. This includes some delegation of director's tasks on the proposed directorial committee (CoDir). Some members of CoDir could support the interaction with the other committees and also be dedicated to IMRB centre activities (e.g., international affairs, advanced training, interactions with industry or core facilities).

Of course, the thematic heterogeneity of such a big centre is a difficulty, but even in the project, the management of the centre is weak or in some aspects non-existent in several domains such as distribution of the budgets and of the technical manpower across the teams, scheduling for scientific applications to ERC, INSERM for instance. The same applies for the distribution of the work spaces and the rules on the use of platforms and core facilities. A real centre policy in these domains should be developed and announced (website). All the instances will have to find suitable ways to apply the strategies of the centre.

The centre pays attention to the emergence of new teams since 2 come from former in-site groups whereas another one is expected to join the centre from outside in 2016.

An effort should be made to quickly gather all the teams at the same place, except the Veterinary School.

Although the scientific activities (conferences, seminars,…) are abundant (not so much at the Department level), there should be several regular cycles of IMRB seminars including seminars of PhDs/postdoctoral fellows (in place); of PI and international invited lectures and also Science & Society.

Assessment of the unit's involvement in training through research

The participation of IMRB teams in advanced training including PhD programs (UPEC, ABIES etc) appears quite productive (91 PhD theses completed in 6 yrs and 73 ongoing at the time of the visit) and multiple MSc programs (Toxicology, environment and health, Physiology and pathophysiology of the cardiovascular and respiratory system", Tissues, cells and genes biotherapies, Immunology).

A member of IMRB is the present director of the Doctoral school "Sciences de la vie et la santé" (ED 402) and has been acting as the director since 2008. This Doctoral school was founded in 2002 and is now unique for health and life sciences of the Paris Est University. About 100 students are welcomed per year including 25 to 35 new entrants. PhD theses, including those performed by physicians, last 4 years at the most. 66 PhDs were working in the IMRB at the moment of the visit. All of them have free access to the INSERM bibliography database; they all attend several seminars every year. Between the 2nd and the 3rd year, students have to pass an examination and finally they must have at least one accepted publication as first author for defence. All the leaders of the INSERM teams are members of the scientific committee of the Doctoral school.

Over the last 5-year period, 90% of the doctors got a position somewhere within 2 years.

IMRB is also actively involved in teaching at Bio-sciences Institute of Paris to train research engineers to be integrated into research teams and the health industries. This seems an excellent source for getting technical staff for IMRB (currently ~1/3 of staff).

The creation of a training program (technical or scientific) specific for post-doctoral fellows could be envisaged, possibly with external funding (Co-FUND, Marie Curie).

Training for security, organisation of the access to the platforms, information about scientific careers, communication between students and between students and seniors should be improved.

Assessment of the five-year plan and strategy

For the next 5-yr period, IMRB proposes to act mainly through 3 main key actions:

1) Improving its scientific structure along the Institute's strongest scientific axes (DHUs); 2/ to continue to developing high-throughput platforms; 3/ to enhance teams' participation in EU projects and industrial funding.

2) The 3 planned actions have their value but the strongest scientific axis has evolved naturally from success to a previous external selective call (APHP/Inserm) for new proposals: the University/Hospital Departments (DHU) call. This led to the creation of the following DHUs: 1) Virus, Immunity, Cancer, 2) Aging, Thorax, Vessels, Blood; and 3) Personalized Neurology and Psychiatry. IMRB proposes some re-structuring according to these 3 new DHUs which seems logical and adequate. Actions 2 and 3 must be now also actively managed.

3) Other changes include the increase in the number of teams to 18; the increase of team interactions through shared PhD students (perhaps the same for post-doctoral fellows should be envisaged), the changes in governance (a new directorial committee - CoDir and Dept councils with monthly meetings) and the update of core-facilites. These all seem quite appropriate.

4 • Team-by-team analysis

Team 1: Translational research in genitourinary oncogenesis

Name of team leader: Mr Alexandre DE LA TAILLE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	8	10
N2: Permanent EPST or EPIC researchers and similar positions		1
N3: Other permanent staff (without research duties)	5	5
N4: Other professors (PREM, ECC, etc.)	4	4
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)	3	
TOTAL N1 to N6	**20**	**20**

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

• Detailed assessments

Assessment of scientific quality and outputs

Research aims of this team are motivated by relevant clinical translational questions related to bladder and prostate cancer (two respective research subgrougs with interesting tools (prognostic biomarkers and new therapeutics and guidelines, unique clinical database and biobanking). The team gathers together scientists and clinicians involved in multiple multcentre European trials. The team performs biobanking with large patient's cohorts (ie: 4500 for prostate), identified and validated biomarkers for prostate cancer diagnosis and treatment (or resistance to treatment) such as PAC3 test, beta-Tub class III, protocadherin PC in castrate resistant prostate cancer, androgen receptor, several chemokine or their receptors. This database is considered as a unique tool. The team further characterized the importance of hormonal environment and correlated the expression of FSH-R on endothelial cells with tumor behaviour (renal carcinoma). Regarding bladder cancer, through a large data base (a national multicentre program), the team validated FGFR3 mutation and correlated the loss of CDKN2A expression with tumor aggressiveness. During 2008 and 2013, they have been associated in 193 papers among which they are the main investigators in a significant proportion (92 as first or last author) (European Urolology, Neoplasia, Cancer research, N Engl J Med, Neoplasia…).

Assessment of the unit's academic reputation and appeal

The team is nationally and internationally recognized for its expertise and this is clearly assessed by the following points :

- The team successfully applied to multiple grants (Investissement d'avenir, COBlance, FP7…).

- The team developed multiple network collaborations (>10) in France, Spain, Greece, Denmark and North America.

- The team organized international meetings, team members are considered as experts in different commissions (PHRC, ARC) and are reviewers or editors in international specialized journals.

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

The team gave multiple national/international invitations (scientific lectures, TV, radio, newspaper).The team has collaboration and funding from industry such as drug companies (Takeda, PFM, Astellas). Three patents have been obtained.

Assesment of the unit's organisation and life

Every other week there is a team meeting in addition to IMRB meetings and others. The team is organized into two subgroups, one subgroup working on prostate cancer and the other on bladder cancer, with respectively 18 and 12 researchers). Importantyly, both are fully connected.

Assessment of the unit's involvement in training through research

During the evaluation period, 15 students made their master, 10 finalized their PhD and 2 are still ongoing. Team members are directly involved in Master 2 Sciences chirurgicales, in M1 and M2 Biologie-Santé (UPEC and IUT) and also in medical school.

Assessment of the five-year plan and strategy

The team project is structured into 5 axes which are:

1) To optimize prostate cancer diagnosis and the cost-benefit of treatment using high-throughput microarray technologies for molecular signatures on samples from a large patient's cohort (biobank) together wit an epigenetic approach (telomere instability and miRNA signature profiles) and proteomic (although not detailed). The role of relevant candidates (ie: miRNA) will be investigated in preclinical in vitro and in vivo cancer models. Possible new therapeutic targets will be investigated. Urinary biomarkers after prostatic massage will be also investigated in

microvesiscules. Alternative new prostate cancer treatments will be validated (inhibitors of nucleophosmin) in clinical trial and new molecules in preclinical animal models.

2) To identify critical molecular signalling pathways involved in the development of prostate cancer. This will be performed with lentiviral technologies (for CAV1 expression) in cell lines (PC3). The CAV1 action will be neutralized through knockdown or siRNA.

3) To investigate the heparin-affin regulatory growth factor (HARP) which plays the role of growth factor for cancer cells and its interactions with extracellular matrix in human prostate cancer. Its interactions with EMMPRIN and MMPs will be deeply studied.

4) To perform a peptidomic analysis to find new pepides that could be either relevant for the treatment of prostate cancer or used as biomarkers.

5) To determine the hormonal profiles in the context of prostate cancer in rodent models. This will allow a better understanding of underlying mechanisms.

Concerning bladder cancer, this particular aspect includes biomarker approaches and molecular taxonomy in large patient cohorts (mRNA, miRNA, immunohistochemistry). This is a direct continuation of what was previously done. In addition, each profile will be correlated with treatment response or resistance (Panitumab). Human tumor xenogafts in mice will be performed in order to investigate the role of Tyro 3, a tyrosine kinase.

Conclusion

- **Strengths and opportunities:**

- This is clearly a promising translational approach based on very large numbers of samples (unique), biobanking and patient databases. This should allow validation/identification of biomarkers in different cancer subgroups with different prognosis and capacity to respond to specific (adapted) treatments.

- The team has a good rate of publications and grants.

- The team is an internationally recognized team.

- **Weaknesses and threats:**

For several aspects of the project, hypotheses seem sometimes too ambitious (on a purely scientific and mechanistic point of view) with different techniques that require high level of expertise such as genomic, epigenetic and proteomic. The project mainly relies on a large biobanking approach which is clearly feasible whereas the underlying mechanistic approach is less clearly assumed.

- **Recommendations:**

- The team should to be more focused on a smaller number of techniques/sub-topics avoiding dispersion, for instance on one set of biomarkers such as miRNA or several proteins or genes, not all together to increase the feasibility of the project.

- The immunological signatures and animal models will benefit from discussion with with immunologists in the VIC department.

- The team has to increase its number of senior scientists.

- The team is encouraged to collaborate with skillful teams in the Ile de France and elsewhere.

Team 2: Immunology and oncogenesis of lymphoid tumours

Name of team leader: Mr Philippe GAULARD

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	8	8
N2: Permanent EPST or EPIC researchers and similar positions		
N3: Other permanent staff (without research duties)	3	3
N4: Other professors (PREM, ECC, etc.)	1	3
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1
N6: Other contractual staff (without research duties)	2	1
TOTAL N1 to N6	**15**	**16**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	6	

• Detailed assessments

Assessment of scientific quality and outputs

The team has developed 3 highly competitive research subjects which are 1) the molecular heterogeneity of diffuse large B-cell lymphomas (characterization, classification and identification of predictive markers); 2) the molecular characterization of peripheral T-cell lymphomas; 3) the normal and pathogenic role of the IL4I1 protein in immune response and immune escape in tumors.

The team has reached an excellent scientific level/output of clinical and translational research with 134 original publications (2008-2013) including 39 as first or last authors (Lancet, Leukemia, Blood, Plos One, Am Surg Pathol, Eur J Immunol , Hum Pathol,…), 30 reviews (19 as first or last authors) and 19 book chapters.

The scientific quality of the translational research performed in this team is recognized by their international leader position in the field and their involvement in international networks.

Assessment of the unit's academic reputation and appeal

Clearly, the team has an international leader position in the field as attested by their international acknowledgement. This expertise leads to involvement in new lymphoma classifications, establishment of clinical recommendations and guidelines It is also attestedd by many presentations at international meetings, invited lectures (invited lectures at UCLA, Stanford University, Taipei, American society of haematology).

The team has an international attractiveness for post doctoral fellows and has been granted for 3 post-doctoral positions.

There are national and international projects with collaborations (Biomed 2, EuroFISH, LLBC…).

The team members are involved as referees in international comittees/institution.

Remarkably, in the past 5 years, the team has been granted for >1.5 ME as external grants.

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

2 patents (2010 and 2013) have been obtained. The team leader is scientific manager of the CALYM (national consortium) labelled by the French Ministry (research and innovation). The team has also an international partnership with economic world (MedImmune USA, Iteos Belgium and Innate pharma (France)). Several training sessions for professionals from the industrial companies have been performed. Also social events have to be mentioned with sport activity from which the benefit is given for research activity.

Assesment of the unit's organisation and life

Weekly technical and scientific meeting is organized with lab members and senior scientists. A specific lab management meeting is also organized. A “green retreat” is annually held. The group is a mixture of pathologists, biologists and immunologists working in lymphoma at the Henri Mondor University Hospital, in collaboration with physicians of the Lymphoid malignancies unit and with lymphomas networks, especially the "Lymphoma Study Association" (LYSA) and the "French study group on cutaneous lymphomas" (GFELC). The multidisciplinary team and the link with clinical trials is essential for the purpose of the team. The group is subdivided into three different subgroups: B-Cell lymphoma, T-cell lymphoma, and Immune escape.

Assessment of the unit's involvement in training through research

Four PhD have been defended during the evaluation period and 2 are ongoing at the time of the visit. All PhD students have published their work in international high impact factor journals.

Senior members of the team have university positions with numerous teaching activities (inside and outside) at multiple levels. There are also a specific national training and post-graduate courses on lymphoma diagnosis and molecular pathology of cancer organized by the team.

Assessment of the five-year plan and strategy

For the next five year contract, two complementary goals are planned:

1) the analysis of molecular alterations associated wth lymphoma entities, mainly PMBL for large B-cell lymphomas (i.e.: STAT6, DLBCL and MALT mutations) and candidate oncogenes (i.e.: ETV1, LMO4, TCF4, miR203) in AITL for T-cell lymphoma. Whole genome sequencing approaches and the possible role of the TCR signalling will be performed in the context of AITL. The underlining mechanisms of TET2, IDH2 and DNMT3A mutations in the development of AITL will be investigated. TFH plasticity and the role of CD10 and PD1 as well as molecular classification of PTCL will be also performed. All these thematics will be developped in collaboration with other teams of the IMRB (thus taking benefit from interactions with other IMRB groups), national and international partners (Rennes, Lausanne, Canada).

2) the characterization of suppressive mechanisms mediated by IL4L1 in relation with immunosuppressive enzymes associated with tumor immune escape particularly in follicular lymphoma. Potential inhibitors of IL4I1 will be sought and tested. The team has applied for an "ANR innovation" grant in collaboration with Strasbourg university.

A clinical and pathophysiological research approach will be carried out in parallel.

Projects are encouraging, realistic and very convincing.

Conclusion

- **Strengths and opportunities:**

- The team has a convincing and original scientific project of high medical relevance with translational research and multiple complementary approaches developed by an expert research team and clinicians.

- The excellence of the team is attested by the rate of publications, the capacity to raise funding and to attract students and post-doctoral fellows togther with international reputation.

- Multiple national/international/intra-IMRB collaborations attest for their attractiveness.

- The team has access to a large pannel of human samples of critical importance in this type of research.

- **Weaknesses and threats:**

The projects of the team are highly competitive.

- **Recommendations:**

The team has to increase collaboration with experimental transplantation team (mouse/human) working on immunomodulation of alloimmunity.

Team 3:

From pathophysiology towards immune---based interventions in HIV infection

Name of team leader:

Mr Yves LEVY

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	6	7
N2: Permanent EPST or EPIC researchers and similar positions	4	4
N3: Other permanent staff (without research duties)	8	9
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	7	6
N6: Other contractual staff (without research duties)	15	16
TOTAL N1 to N6	**40**	**42**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	5	
Theses defended	9	
Postdoctoral students having spent at least 12 months in the unit	7	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	4	

• Detailed assessments

Assessment of scientific quality and outputs

The team has been working on the topic of HIV disease for a number of years and has gained a major visibility in this field. In particular, the team has focused on the exploration of the pathogenesis of HIV disease, on the possibility of modifying its progression with biological agents (IL-2, IL-7) and on the development of vaccines for this disease. These efforts have led to the team becoming probably the most prominent in France and one of the most visible on this particular topic of research on a world wide-basis. The team has played a major role in one of the most complex and expensive clinical trials that has ever been organized in the field of HIV medicine: namely the verification of the possible beneficial effects of interleukin-2. Unfortunately, the results were negative (i.e. IL2 does not change the prognosis of patients), but the trial yielded a considerable amount of scientific knowledge that has been useful in many basic and clinical research fields. The team has also done a very good work in clarifying the role of Treg cells in the progression of HIV infection. The main actual collaborations are with clinical/research/vaccine sites in Switzerland (Lausanne) and in the US (Dallas).

The scientific output is witnessed by the impressive amount of papers, often of good quality, and of patents : 151 original articles in international peer-reviewed journals (71 with a team member as first and/or last co-author) with high impact [Clin Inf Dis 2012; Mol Cell 2012; PloS Pathog 2011; PNAS 2010, N Engl J Med 2009], 26 review articles (25 with a team member as first and/or last co-author) and 14 international patents with team members as inventors or co-inventors. Among the papers published in the period 2008-2013, 2 articles ranked with IF>20; 5 articles with IF between 15 and 20; 4 articles with IF between 10 and 15 and 27 articles with IF between 5 and 10.

Assessment of the unit's academic reputation and appeal

The academic reputation of this research team is excellent. This is witnessed by the collaborations that the team has established with leading research organizations world wide (e.g. Gates foundation) and by the fact that the team leader as well as many of the team's components have received a number of invitations to present their data at international meetings. The team has also been able to recruit a number of professionals, PhD students and post-doctoral fellows in the period examined, again indicating its attractiveness toward the scientific community. The team has been exceptionally succesful in winning grant money. The submitted document does not provide much information on the participation of the team members to editorial boards and the eventual bestowing of awards.

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

This parameter is satisfied by the important role that team members play within SIDACTION and AVAC. The team leader is one of the main consultants on the topic of HIV disease for the French goverment and is one of the most visible French scientists dealing with this aspect. The team leader and many of the team's members are involved in the cultural and the social environment and are well known within the patient's community; their visibility within the lay press is very high.

Assesment of the unit's organisation and life

The team is divided into 4 different subgroups (immune restoration, immune regulation, immune intervention, Baylor Research Institute (BRI) that are smartly designed and continously interacting. This is an intelligent way to optimize and finalize the specific competences that each of the members of the team has. The team has also started, and coordinates, both the MIC, an immunology reference lab within the Institute, and the Vaccine Research Institute (VRI), a vaccine development-oriented subunit. It is to be assumed that all these components interact scientifically in the best way. The submitted document does not provide detailed information on the management of the day by day life of the team and the management of human and technological resources and this has not been clarified during the visit.

Assessment of the unit's involvement in training through research

Although this is clearly a mostly clinical research-oriented team, the components do a pretty good job in basic training as well. This is witnessed by the observation that one of the team members heads a Master immunology program at Paris 11 University and is co-responsible for developing all the aspects of teaching in the medical school at

Creteil. The team's strength in this particular aspect is also confirmed by the attractivity that the team has towards PhD and post-doctoral fellows, many of which became authors of good papers. 9 PhD theses have been defended during the examined period and 5 more are in preparation; many of the PhD students are from abroad.

Assessment of the five-year plan and strategy

The team's general objectives in the next 5 years focus on achieving a better understanding of the basic immunopathogenesis of HIV infection and to develop novel vaccinal and therapeutic options for this disease. The team will focus a good amount of its efforts on mucosal immunity and on the analysis of how it correlates in pathology in non human primates (NHP). The idea of focusing on mucosal immunity (and possibly, on mucosal vaccines) is indeed interesting. The committee was a bit more skeptical on the willingness to focus on NHP due to specificities such as variety of animal species (risky considering the raise of violent animalism in Europe), of virus, and of diseases. A possible criticism stems from the fact that it was not overtly clear which of the numerous candidate vaccines would be developed; the idea of pursuing 4 or 5 different approaches could be a bit overambitious and that part of the presentation lacked some focus.

Conclusion

- **Strengths and opportunities:**

- The team is an excellent actor in the field and is dynamic and enthusiastic despite the negative results of the massive IL-2 clinical trial.

- The team leader is an outstanding leader of opinion.

- The idea of creating the BRI and the VRI is very smart.

- **Weaknesses and threats:**

- The vastity of the team program (basic science, development of candidate vaccines, clinical program, the use of innovative methodologies) represents a potential threat.

- The research plan is very strong with minor potential problems identified :

1) The committee is not convinced about the NHP aspect for scientific, economical and "social opportunity" reasons (in Europe the pro animal life organizations that oppose animal experimentation are getting more and more violent and gain support; maybe it is not the best idea to work with monkeys).

2) Some decisions should be made as far as which line of HIV vaccine should be carried on; it might not be the best strategy to develop all of the 4 or 5 there were presented.

3) A final philosophical potential critique may be that it would be interesting to differentiate a bit and consider starting lines of research on pathologies other that HIV since the team has the knowledge of basic human immunopathology, the intellectual curiosity and the fire power to do that.

The timing for the construction of the new VRI building is key for the success of the programme.

- **Recommendations:**

The team must strive to maintain the focus and constantly adapt objectives and strategies.

Team 4:

Pathophysiology and therapy of chronic Viral Hepatitis and related cancers

Name of team leader:

Mr Jean-Michel PAWLOTSKY

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	8	12
N2: Permanent EPST or EPIC researchers and similar positions		1
N3: Other permanent staff (without research duties)	6	6
N4: Other professors (PREM, ECC, etc.)	1	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2
N6: Other contractual staff (without research duties)	7	4
TOTAL N1 to N6	**24**	**25**

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

• Detailed assessments

Assessment of scientific quality and outputs

The research activity of the team has focused on two main themes: a) the HCV drug development and the study of the molecular mechanisms that affect the outcome of treatments for hepatitis C, including viral heterogeneity and viral resistance; and b) the molecular mechanisms responsible for the progression of virus-induced hepatic and extra-hepatic lesions, including steatosis, insulin resistance/diabetes, fibrosis and liver cancer.

The team has been in the forefront of the new HCV drug development with a broad translational research approach ranging from the design and participation to large clinical trials, to clinical investigation, molecular virology and drug design. The main achievements, reflected in high impact publications and the filing of several patents, are: a) over 700 patients included in Phase I to IV clinical trials with new HCV drugs; b) the characterization and validation of virological, genetic, immunological and environmental predictors of HCV treatment outcomes [N Engl J Med 2009, Gastroenterology 2011; Lancet Infect Dis 2012; J Hepatol 2013]; c) the development of original approaches based on next-generation sequencing and sequence data analysis by means of an in-house protected software package (Pyropack© patent) and application to the study of viral resistance to antiviral drugs [Hepatology 2013]; d) the development of new antiviral approaches based on inhibition of HCV RNA polymerase by natural phenolic compounds, including silymarin and aurone derivatives (patented) [Gastroenterology 2010; J Med Chem 2011]; e) the development and characterization of the biochemical, virological, pharmacological and toxicological properties of new cyclophilin inhibitors with potent anti-HCV properties through a fragment-based drug design approach (patented). This research activity led to an unexpected and yet very interesting development with the evaluation of one specific anti-cyclophilin compound with selective anti-cyclophilin D activity in cardioprotection after myocardial infaction (team in the PhyDes department at IMRB).

The team research efforts on the pathophysiology of HCV-induced extra-hepatic disorders and the progression of HCV-induced liver disease have been highly productive as well, as documented by a large output of relevant high impact publications in the context of highly competitive fields. The most important findings are: a) the characterization of HCV-NS5A protein transactivating properties and the impact on the regulation of HCV replication [J Virol 2013]; b) the demonstration in HCV transgenic mice, that HCV-associated triglyceride accumulation in hepatocytes is linked to defective secretion of VLDL, as a result of a decrease in microsomal triglyceride transfer protein activity and the direct activation and nuclear translocation of SREBP1c [JBC 2009]; c) the identification of an HCV-driven IL-6-dependent impairment of insulin secretion and insulin resistance of both muscular and hepatic origins in HCV transgenic mice and infected patients; d) the demonstration of a direct role of HCV proteins in inducing hepatic fibrosis in the absence of HCV infection of hepatic stellate cells [J Hepato 2012]; e) the characterization of the direct role of HCV in liver carcinogenesis mediated by: 1. a diminished Gadd45 beta expression secondary to the hypermethylation of the Gadd45 beta promoter, that leads to aberrant cell cycle arrest and diminished DNA excision repair [Can Res 2010]; 2. an increased c-Myc expression [Oncogene 2012]; 3. AKT activation by NS5A and the subsequent stabilization of the transcription factor beta-catenin [Oncogene 2012]; 4. Bid degradation by a calpain cysteine protease activated by NS5A.

The overall output is 159 articles in international peer-reviewed journals, 23 articles in French peer-reviewed journals, 20 book chapters, 2 patents on new antiviral drug families and 7 protected softwares on next-generation sequencing interpretation. The team has authored an impressive number of critical reviews and invited editorials in high impact journals.

Assessment of the unit's academic reputation and appeal

The team is internationally recognized as a world leader in viral hepatitis research, as illustrated by 271 invitations to give lectures abroad between 2008 and 2013. The team leader has served as Secretary General of the European Association for the Study of the Liver-EASL (2005-2009); Associate Editor of Hepatology (IF 12.0), 2001-2005; Associate Editor of Gastroenterology (IF 12.8), 2010-2015; Chairman and organizer of the 16th International Symposium on Hepatitis C Virus and Related Viruses, Nice, 2009. The team leader is the President of the Scientific committee 4 (Basic Research in Viral Hepatitis) and leads the Concerted Action 33 at the National Agency for Research on AIDS and Viral Hepatitis (ANRS). The team hosts the French National Reference Centre for Viral Hepatitis B, C and Delta, with team members as director and deputy director. The team is also part of the Vaccine Research Institute (VRI) “Labex” (Network of Excellence), funded as part of the “Investissements d’Avenir” programme, headed by Team 3 leader.

The high reputation of the team is reflected by an increasing attractiveness and the number of lab members has substantially increased during the 2008-2013 period. Two scientists (PUPH) joined the team; two engineers were recruited on permanent positions and two post-doctoral fellows were recruited on competitive fellowships. In addition, the team has managed to be funded to support both the renovation of the lab space and a substantial upgrade and expansion of the laboratory equipment, including NGS.

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

The team has several contracts with industries on hepatitis virus resistance to antiviral drugs and next-generation sequencing and generated patents on new anti-HCV drugs in collaboration with INSERM-Transfer and on innovative softwares for NGS-data analysis.

Team members have actively participated to the redaction and dissemination of the EASL Clinical Practice Guidelines for Hepatitis B and Hepatitis C that had a very important impact on the access to cures and the managenent of HBV and HCV patients throughout Europe and beyond.

The team leader has participated to high audience media programs on France Inter radio (2008) and Radio France International (2009) and press interviews (Le Figaro, 2011).

Assesment of the unit's organisation and life

The team organization appears to be straighforward with a successful blend of strong leadership and sharing of day by day managenent duties as well as strategic decisions among the senior members of the team, based upon competence and scientific arguments rather than the position held. All team members, including students and technical/administrative staff, participate to the lab life through frequent and regularly held scientific and organizational meetings.

Assessment of the unit's involvement in training through research

The team has been quite active and successful in research training both at the PhD (7 students) and in Master [M1 and M2] (8 students) level. PhD students have all been highly productive and published substantially. Importantly, all the 4 PhD students that have completed their thesis now have jobs/positions in research. Many of the team members teach and lecture extensively.

Assessment of the five-year plan and strategy

The strategic plan for the next five years is largely embedded into the project of the VIC Department, that is part of the IMRB, as well as into the more global project of the VIC DHU, also directed by the team leader, whose aim is to create a centre of excellence in care, research and education focusing on viral infections, cancers, immunity and their relationships. In this perspective, the team has established extensive collaborations with clinical and research teams belonging to the VIC DHU and is taking an active part to the building of that project.

The research efforts will be directed in two directions: a) the development of new antiviral and vaccine approaches for HCV and related viruses; b) the understanding of the molecular mechanisms of HCV disease progression and HCV-related hepatocarcinogenesis.

The first axis will focus on: 1/ the clinical development of new antiviral and vaccine approaches for HCV infection by characterizing the mechanisms of treatment/vaccine success and failure in order to optimize future therapeutic and preventive approaches; and 2/ to identify and fully characterize new targets for antiviral intervention and new therapeutic approaches for HCV and related viruses. New drug and vaccine trials will be performed by the clinical structure, directed by one team member. The clinical virology subgroup will be in charge of the virological studies for clinical trials and the large ANRS HEPATER cohort (25.000 patients), for the development and application of NGS-based protocols for the study of viral heterogeneity and resistance and, on a more mechanistic basis, will continue the investigations into the mode of action of ribavirin. The experimental virology subgroup will work on the identification of the 5' and 3' untranslated regions of HCV and related viruses RNA as targets for antiviral interventions and will continue on the optimization and characterization of the antiviral properties of new cyclophilin inhibitors, including the identification of additional viral targets.

The second, and more strategic effort (mechanisms of HCV-related hepatocarcinogenesis (HCC) and development of new preventive and curative approaches for HCC) will be devoted to: 1/ unravel the molecular mechanisms by which HCV directly triggers the liver carcinogenic process and understand the influence of non-viral factors frequently associated with chronic HCV infection; 2/ to understand the role of the immune microenvironment in HCC progression and resistance to current anti-cancer therapies and the molecular mechanisms involved. To fullfill these aims, the clinical structure has been significantly reinforced by the recruitment of several senior physicians/scientists [2 senior hepatologists, 1 liver surgeon, 1 pathologist and 1 radiologist] and the experimental group has been substantally enlarged and potentiated by the incorporation of three experienced scientists in the field of liver inflammation and immunology and their collaborators. The specific aims of the HCV-HCC subproject are to: a) study in TG and GM mice the effect of HCV on the Pi(3)K/AKT pathway; b) characterize in cell and mouse models the mechanisms and consequences of the modulation of the oxidative stress-DNA damage-cell cycle axis by HCV protein expression; c) to study the role of disease progression co-factors (diet, inflammation, lipid and glucose metabolism) in HCV-induced HCC; d) to investigate using both genome-wide chromatin immunoprecipitation and functional approaches, the role of HCV NS5A protein transactivation in the liver carcinogenetic process; e) to study the role of the liver immune micro-environment in HCC progression and resistance to current anti-cancer therapies with a focus on the ability of IL17-producing T cells to sustain Cancer Stem Cell (CSC) self-renewal and M2 to M1-like macrophage phenotype switching in the resistance to sorafenib treatment.

Overall, the research plan shows a clear strategic vision with an effort to capitalize and continue the research trust on HCV cure and, at the same time, refocus and reinforce the expertise and the manpower to work successfully on HCV-related HCC, a field that is extremely competitive both at the french and the international level. The research plan is quite well structured. It builds upon the strengths of the team but is not limited to the continuation of existing lines of research, albeit fruitful in the past. One open point is whether and when the team will consider to orient its competence on HCV molecular virology, drug hunting, cell-based viral replication systems and animal models expertise to tackle HBV-cure and HBV-carcinogenesis, the new strategic unmet medical need in viral hepatitis research.

Conclusion

- **Strengths and opportunities:**

- The team is internationally recognized, very productive, attractive for national and international scientists and students, well inserted in the local, national and international environment with strong influence on the international research landscape.

- The team members have strong experience and diverse complementary skills and this has proved crucial to perform true translational research from the bedside to benchside and benchside to bedside. The IMRB Research Centre and the VIC-DHU provide all the needed core facilities, synergies and direct access to patients. The incorporation of new scientists coming from another team will broaden the expertise and the scope of research of the team.

- The scientific program is solid and bears a high likelihood for success. The re-focusing and extension of the “pathophysiology” research activities on hepatocellular carcinoma (carcinogenesis, tumor progression and therapy) is clearly strategic.

- **Weaknesses and threats:**

Potential threats are represented by:

- the fast growth of the team and the need for a strong effort to fully integrate new team members;

- sustaining the innovative nature and the productivity of the research program while moving further into the very competitive field of liver carcinogenesis and HCC management;

- the need for more permanent positions at the technician/engineer level.

The very successful management of the team during the past 5 years cycle should ensure that these potential weaknesses will be dealt with the required vision and leadership.

- **Recommendations:**

- The team may actively pursue the recruitment/stabilization of the existing senior scientists that already lead successful and strategic research projects.

- The policy of further reinforcing the team “pathophysiology” research subgroup by recruiting/attracting more manpower with complementary expertises has to be envisioned.

- The team has to consider a further strategic move into the HBV field (“HBV cure”) recognized, together with HBV/HCV- associated hepatocellular carcinoma, as the new strategic aims in hepatitis research.

Team 5: Renal immunopathology and transplantation

Name of team leader: Mr Djillali SAHALI

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	10	10
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)	2	2
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1
N6: Other contractual staff (without research duties)	3	3
TOTAL N1 to N6	**17**	**17**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	6	

• Detailed assessments

For historical reasons the team is divided in 2 sub-teams: the first (the oldest) working on translational research in renal immunopathology, the second that only recently joined the group, is working on clinical and experimental alloimmunity and transplantation. Importantly, both sub-groups have important implications in the clinic (bedside to bench approach), although the link between the two teams does not appear to the committee.

1) Regarding renal immunopathology, research topics are focused on the effect of c-mip in either podocytes or T cells. Overexpression of c-mip induces proteinuria and nephrotic syndrome. Receptor tyrosine kinase inhibitors (RTKI) used in cancer therapy also induce proteinuria and a c-mip upregulation allowing to study mechanisms by which proteinuria is induced in these conditions. This is relevant to understand these mechanisms since this is a major side effect of these drugs. By using transgenic animals and sophisticated approaches, it has been shown that c-mip prevents nephrin phosphorylation and induce cytoskeleton dizorganisation (podocytes). Investigation of the cross talk between c-mip and NF-KB is also an important part of the project. This expertise of c-mip has been developped by two PI with high quality publications in the 2000.

2) Regarding translational research in transplantation, this is focused on solid or hematopoietic stem cell transplantation and results from the merge of Mondor and La Pitié teams. Topics include the understanding of the molecular mechanisms leading to allograft rejection or graft versus host disease (GVHD) versus allotolerance as well as the development of immunomodulation strategies relying on the use of Foxp3+ regulatory T cells.

With renal transplant patients, a trancriptomic analysis of intragraft mRNA (predicitive or diagnostic marker) has been developped in several pathological conditions. In another project, the use of aopoptotic cells (obtained by ECP) is combined with face transplantation in order to facilitate allotolerance with an associated mechanistic approach, which is a unique opportunity. In a third transplantation project, the effect of Belatacept (CTLA4Ig), a blockade of the costimulation of B cell alloreactivity is investigated (Bellatacept-treated patients display a lower level of alloantibodies) and particularly through a possible effect of HLA-G upregulation. A four very elegant project is based on the in vitro expansion (before tranfer) of “exogenous” Foxp3+ Tregs that are specific for a recipient-unrelated antigen avoiding the generation/contamination of effectors. In the context of a translational approach and Tregs, the work published in Science Translational is remarkable. This is accompagnied with significant experimental expertise (sophisticated rodent models or immunodeficient animals) as well as academic and industrial financial support.

Each sub-team has published original papers as main investigators (first and/or last authors) in the best journals in their respective speciality. For the Nephrology subgroup, there are multiple papers in Kidney International, Blood, Sci Signal, J Am Soc Nephrol, Am Journal of Pathology, PlosOne, Transplant Int. For the Transplantation subgroup, papers have been published in Science Translational, Am J Transplant, J Am Soc Nephrol, Transplantation, Bone Marrow Transplant, Europ J Immunol, J Immunother, Biol, Blood Marrow Transplant, Clin J Am Soc Nephrol, Nephrol Dial Transplant, Transpl Immunol and J Exp Med, J Clin Invest, J Immunol...

Assessment of the unit's academic reputation and appeal

The nephrology subgroup is recognized as a national reference centre for idiopathic nephropatic syndrome by the Health Ministry and is involved in many different clinical trials (academic) and received several awards. This subgroup has obtained PHRC on clinicopathological correlation of c-mip expression in glomerular diseases, PHRC on the effects of Rituximab in steroid dependent nephrotic syndrome, MSN project (as co-investigator) The subgroup related to transplantation work is involved in many national projects or networks (ANR, RIB, PHRC, PHRC/INCA...)

Organization of international congress (Buenos Aires) has been achieved.

Team members in both sub-groups were invited at multiple conferences (American Society of Nephrology San Diego 2009; ERA-EDTA Paris 2012; International conference for membranous nephropathy, Bergame; Immunology from bench to bedside First Franco Argentine congress in immunology, Buenos Aires 2010; Congress of the American Society of Gene and Cell Therapy Seattle, 2011).

One of the PI is the vice-president of DIM (field of major interest) in biotherapy.

The team leader is Associate editor in transplantation journal.

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

There are several industrial partnerships such as Xgen (phase 1 study) and others (Roche, Novartis, Amgen).

The ExoTreg finding was patented, and financially supported by SATT IDF INNOV.

The team has disseminated its scientific results through TV for face transplantation, France 5 for clinical trial (Le Monde...).

Assesment of the unit's organisation and life

As mentioned above, the team is structured into two subgroups of research, each one having a lab meeting twice a week.

Assessment of the unit's involvement in training through research

Many PhD students have been supervised. 6 PhD defenses have been achieved during the evaluation process and 2 are ongoing.

One PI of the team is the current director of the department of master, co-director and future director of the PhD school n°402.

Team members are heading Masters in Immunology (UPEC), Tissue cell and gene biotherapies (UPEC), cell biology, blood cell biology and make tutoring in licence “immunochemistry and molecular biology”.

The team participates in national training networks (DESC in immunopathology, Master of “Relations hôte-greffon”, DIU of biotherapy) and in international training networks.

Assessment of the five-year plan and strategy

Regarding renal imunopathology subgroup, the project is to characterize the role of c-mip signaling in podocytes, its regulation and study of KO animals and to develop specific inhibitors of c-mip. The study of proximal signaling pathways (Akt-mTOR) in podocytes and lymphocytes will be performed with the development of tissue specific conditional c-mip KO mice. Also, potential c-mip inhibitors (including drugs) will be tested in vivo and in vitro by FRET or BIACORE techniques. Along the same line, techniques using vector based RNA interference will be tested. Intensive collaborations with the hematology department and oncology departments from multiple hospitals have been developed. In the clinic of idiopathic nephrotic syndrom (INS), a proteomic approach of secreted products by B and T cells from relapsing patients will be compared with control T and B stimulated cells. Then, candidate molecules will be tested through new ELISA assays in the blood of patients. In parallel, functional tests will be developed in vitro to understand the effect on cytoskeleton of podocytes as well as in murine models. This is an example of excellent translational research. Phenotypic and functional analysis of regulatory B cells in the INS will be investigated, particularly after anti-CD20 mAb treatment in INS patients as well as in patients with humoral rejection. The molecular mechanisms of Receptor tyrosine kinase inhibitors (RTKI) on podocytes will be also investigated in a separate subproject.

Regarding translational research in transplantation (TRT) subgroup, they will take advantage of a unique gathering of clinical and experimental platforms. As already mentionned, an heavy activity in all types of transplantations is performed on the site of Henri Mondor hospital. Interestingly, the centre for clinical investigation in biotherapy and the Etablissement Français du Sang allows immunomodulation strategies based on cell therapy. Multiple approaches will be developed including a transcriptomic approach of urinary cells (mRNA) in renal transplant patients. Results of specific mRNA clusters (humoral or NK cell responses…) will be confronted to clinical database.

Other projects, based on the strong expertise in Treg, exo-Treg, apoptotic bodies and haematopoietic stem cell transplantation to induce transplantation tolerance, will investigate or will use the imunomodulatory capacities of manipulated Tregs or expanded Tregs in preclinical animal models or in the clinic. Allogeneic skin graft models or liver tranplant models with low dose IL-2 and rapamycine will be performed to investigate mechanisms of tolerance (versus rejection mechanisms). After non human primate models using apoptotic bodies (EP) as immune modulators, a phase 1 clinical trial will be started with renal transplant living donors. In cancer, a PHRC-INCA funded clinical trial based on Treg depletion strategies in the field of human stem cells (HSC) transplantation or donor lymphocyte infusions (DLI) will be performed after CD127+ positive cell selection (instead of CD25). Collaborations with a team in

Hannover will allow selection of antigen specific Tregs. Several drugs (HMG-Coa reductase inhibitors, CNI) will be tested for modulation of the positive crosstalk between innate and adaptive immunity in experimental models of liver ischemia reperfusion injury and subsequent alloimmunisation as the impact on Treg homeostasis.

By this aspect, the whole project is unique by gathering exceptional human resources: liver transplant, international experts in kidney transplantation with a significant activity (impressive number of transplantations/year) and consequently large patient cohorts and innovative protocols of haematopoietic stem cell transplantation.

Conclusion

- **Strengths and opportunities:**

- This represents a unique context on the same site (big and acknowledged clinical activity of various transplant medicines, haematology with EFS and allogeneic HSC transplantation) with strong and recently expanded scientific and experimennal expertises. This allows translational research as underlined by the team projects and the collaboration between the different units (ie CIC-BT).

- The team (at least the transplantation sub-group) is new and promising approaches are described.

- There is a wish to expand (space, number of researchers,…). Each member has proven his scientific capacities by the quality and number of previous publications.

- The environment is rich in experimental models and platforms with a strong implication in training with PhD students, post-doctoral fellows and HDR involved in the clinic too.

- **Weaknesses and threats:**

- Although respective projects (nephrology or transplantation) are very interesting and pertinent, the committee underlines the poverty of a single dynamic and got the feeling of a fusion of two nearly unrelated subgroups (even for historical reasons) rather than a single team.

- There are insufficient collaborations in international networks.

- There are many difficulties for funding in experimental transplantation.

- **Recommendations:**

Relations and synergies between the 2 subgroups should be strengthened and should appear more clearly as a driver that justifies the build of a single team.

Team 6: Interventional neuropsychology

Name of team leader: Ms Anne-Catherine BACHOUD-LEVI

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	2	3
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)	3	3
N4: Other professors (PREM, ECC, etc.)	1	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	3
N6: Other contractual staff (without research duties)	2	3
TOTAL N1 to N6	**11**	**13**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	

• Detailed assessments

Assessment of scientific quality and outputs

This team performs clinical research in a very original and innovative niche that stands at the interface between cognitive neuroscience and functional intervention in brain diseases. The team has extended its scope in cognitive neuroscience from well-established frameworks of the neuroscience of language to less chartered domains that cover communication in general. The latter involves non verbal communication and by essence implies social cognition aspects, i.e. moving the focus from subject-centred approach to dual or multiple interaction amongst individuals. From the point of view of brain disease, the bedrock of the team work is traditional lesion-based neuropsychology and the study of the relationships between damage to specific brain structures (eg. Striatum) and cognitive functions, here, mainly language. The team has taken the opportunity of its involvement in cutting-edge therapeutic strategies in highly specific patient samples,such as for example fetal neural tissue grafting in Huntington's disease (HD), to develop innovative research line in terms of tissue/function restoration in brain damaged patients with a special emphasis on damage to the striatum. An important research line throughout the team project is the implication of striatum in human communication. The team has and will benefit a great deal of its long established collaborations with neuroscience and neurosurgery teams that are in the Mondor/Paris environment and for some are part of the current Centre project (team 9).

The team has been very productive in terms of publications, with articles published in journals of good to outstanding visibility. As described in the team report, the counts are 84 original articles and 7 reviews with 47 papers in first or last author position. 2 papers have been published in Lancet, New Engl J Med, and the rest in journals which IF ranging from good to excellent. Approximately 10 papers were published per year over the past contract time and the team leader has overall a h index of 27 and has received about 200 citations per year over this time. Not only the team leader but also her co-workers and students are in strategic positions (either first or last) in the author list, witnessing that the respective contribution of collaborators is well acknowledged. For most of them, publications are central to the team research lines, namely Huntington's disease and cognitive neuroscience of language.

Assessment of the unit's academic reputation and appeal

The team, its PI and her co-workers has excellent visibility especially in the domain of clinical studies and interventions in Huntington's disease patients and in some aspects of the neuroscience of language. Research of the team and of the team leader especially is heavily linked to those of Department of Cognitive Studies at the Ecole Normale Superieure as an individualized team of this Department (Neuropsychologie Interventionnelle). Among other grants, the team benefits from a Labex grant obtained by one PI from the ENS Cognitive studies department.

The team has attracted more than 5 PhD students in the recent years and 3 post-doctoral fellows are or will contribute to the research.

Over the past contract period, team members received 37 invitations to address international conferences, mostly in the field of Huntington's disease clinical studies and often in the context of European origanizations such as the European network on HD that the team leader has contributed to create.

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

A number of communication activities are described towards various media, participation in radio and TV programs, general audience conferences. Strong link with Huntington's disease patient association and participation to Telethon have to be mentioned.

Assesment of the unit's organisation and life

The activities of the team are divided in typical clinically-oriented work and more fundamental activities in the field of cognitive neuroscience. The team is organized in 3 subgroups headed by a PI including the team leader and covering verbal communication, non verbal communication and degeneration and reparation, respectively.

Assessment of the unit's involvement in training through research

The team participates in bachelor and Master-level teaching in Medicine, Psychology and Cognitive Sciences (University and Ecole Normale Superieure) as well in PhD students supervision in the Creteil as well as in the ENS.

Assessment of the five-year plan and strategy

Future research will be in line with previous activities that will be organized according to the structure of the team in 3 subgroups addressing verbal communication, non verbal one and restorative strategy. The verbal communication projects focuses on the role of the striatum in specific language-related functions such as rule learning, syntactic ambiguity resolution, selection of responses, these roles being respectively exclusive according to the authors. Extending their approach from language-based to non-verbal means of communication, the members of the team involved in a dedicated sub-group dealing with non-verbal communication will explore first-, second-, and third-person social interactions in relation to the activity of striatum and its damage such as in HD; various methods of behavior measurement will be used such as psychophysics, EMG and eye-tracking. Finally, restorative research will capitalize on the unique experience based on the pioneering activity in grafting fetal striatal tissue in HD patients (MIG-HD program). In addition, remediative project will be developed to try and alleviate specific communication disorders in patients identified in the previous studies.

Very recent publications demonstrated the major interest of gene therapy in Parkinson's disease. It will also relate to the strong interactions with other teams of the centre in the domain of psychiatry (Team 8), neurosurgery (Team 9) and interventions (the one which will join in 2016).

Conclusion

- **Strengths and opportunities:**

- The team has a unique experience in the field of the communication disorders (both verbal and non-verbal) observed in patients with striatum pathology, especially HD. Its strong and long established collaborations with other teams in Creteil for the clinical component of its research and with renowned groups in cognitive neuroscience especially at the ENS is a major advantage for the team.

- The team leader was highly successful in developing the interface between clinical research and cognitive neuroscience and there is no doubt that this strong interaction will continue to be extremely fruitful.

- **Weaknesses and threats:**

- The team in its inner organization is relatively poorly staffed and recruitment of new collaborators, scientists as well as technical staff shoud be encouraged.

- One potential limitation is for the team to remain centered on the HD model although its pioneer role in this field implies the maintenance of on-going (long lasting) clinical trials that are by essence time- and energy- consuming and require specific organization and staff.

- **Recommendations:**

By its originality and high potential to put forward new hypotheses and innovative research strategies, the team will be a major partner of the neuroscience component of the Creteil Centre. There is little doubt that the team will also develop new collaborations in closely connected fields, including in the Centre itself such as with team 8.

Team 7: Biology of the neuromuscular system

Name of team leader: Mr Frederic RELAIX

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	7	17
N2: Permanent EPST or EPIC researchers and similar positions	1	5
N3: Other permanent staff (without research duties)	2	24
N4: Other professors (PREM, ECC, etc.)		3
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		9
N6: Other contractual staff (without research duties)	2	5
TOTAL N1 to N6	**12**	**63**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	7	
Theses defended	8	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken	6	
Qualified research supervisors (with an HDR) or similar positions	13	

• Detailed assessments

Assessment of scientific quality and outputs

Five previously independent research groups contribute to the team Biology of Neuromuscular system that will be directed by F. Relaix. During the last 5 years, the scientific production of the different groups was in general at a very good level (in total 243 articles including 41 reviews) with several publications in highly ranked journals including Developmental Cell, Genes and Development, Nature Genetics and PNAS, but also a large number of publications in more specialized journals (Exp Cell Res, J Cell Biol,...). The team leader subgroup is a highly dynamic young team (INSERM Avenir group at Myology Institute) working on Pax3/Pax7 functions during skeletal muscle, neural tube and craniofacial development. This group uses large collection of genetically modified mouse models and applies large-scale genomic approaches. The research spectrum of this subgroup during last period was relatively large encompassing 7 different topics. The amount and quality of generated data suggests it will be at the origin of several additional publications. The subgroup working in the field of neuromuscular disorders has developed particular research axes on Myotonic Dystrophies with "DM-scope registry" and development of in situ hybridization as a marker of DM severity but also on Macrophagic myofascitis. This subgroup also investigates the role of myofibrosis in motor disabilities in Duchenne muscular dystrophy and is studying different cell therapy strategies including role of pericytes in postnatal muscle growth and regeneration. The third contributor of the new team is the subgroup working with dog and cat models of human genetic diseases. Among others, they characterized centronuclear myopathy in Labrador retrievers and identified disease causing gene. Dog and cat models of human myopathies including centronuclear myopathy and dystrophinopathy are also investigated by an other subgroup. This group contributed to cell therapy approaches conducted on dog models in collaboration with a team in UK (UCL, London) and to exon skipping approaches in collaboration with a PI in Généthon (Evry). The expertise of the last two subgroups appears to some points redundant but their individual contributions to the proposed future projects are clearly defined. Finally the last subgroup conducts research on tissue engineering for bone repair. This group has an original expertise which represents an interesting extension to be applied to tissue repair approaches of neuromuscular system providing an additional value to the team.

Assessment of the unit's academic reputation and appeal

All PIs are highly recognized in their respective fields. The team leader and the team member heading the subgroup in the field of neuromuscular disorders are regularly invited as speakers for international conferences and meetings and act as experts in highly ranked journals and funding bodies. Both PIs are former members of INSERM CSS2. A team member acts as expert for the French AERES, the UK Welcome Trust and the Belgian FNRS and was involved in international collaboration programmes including European FP7 (LUPA – 12 countries) and PHC Alliance (France-UK). An other is elected member of CNECA commission no.8 and is part of Labex REVIVE network, whereas one participates in two European FP7 projects REBORN and CASCADE. Members of contributing subgroups presented their work in 114 oral communications. They are members of 2 strategic large-scale funding initiative "Investissements d'Avenir" and obtained 51 public and associative grants.

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

The team in total produced 6 patents, including one licensed. CIFRE contracts have been obtained with Antagene company and with Servier to study therapeutic potency of RYCAL stabilizer in dystrophic dogs.

Assesment of the unit's organisation and life

As this is a new entity, the organisation of the life of this team cannot be assessed. Plans for interactions between team members and weekly team meetings are expected to build the cohesion of this large team.

Assessment of the unit's involvement in training through research

All group leaders were involved in PhD and master student trainings as well as in teaching in PhD programs. In total, 8 PhD students defended their thesis trained during the last period and 7 are ongoing and the team members participated in 16 PhD and 9 HDR juries. It is important to notice the high number of HDR holding researchers (13 in total) which makes the team highly attractive to PhD students. The team leader actually INSERM researcher, is in the process to become University Professor so will have some teaching activities with an opportunity to identify and to attract talentous students.

Assessment of the five-year plan and strategy

The proposed research strategy is based mainly on ongoing individual projects of team members. It is subdivided on 3 sections encompassing research activities of all contributing subgroups and comprising i) clinical research in neuromuscular diseases; ii) basic research of the neuromuscular system and iii) translational research for neuromuscular diseases. Here, a large set of experimental approaches is proposed. This part of proposal is presented without indications who within this large team will perform different experiments so that it is relatively dificult to assess respective contributions of individual team members, however in general proposal appears highly ambitious and compatible with different skills present within the team. Importantly, team members will also develop integrated research projects based on complementarity of interests and already initiated interactions. One highly innovative project with common interest of several members of the new team is the generation of novel large animal neuromuscular diseases (NMD) models and in particular the dog model. This will imply isolation and establishment of ES cells from dog blastocysts followed by standard genome modifications mastered by the team members but also using novel genome editing approaches (TALEN, CRISPR/Cas9 strategies). A partnership with external funding agencies such as AFM is planned to develop this project. An important issue that should facilitate to build cohesion within this large team is a common interest in translating the high standard fundamental research performed by the team leader subgroup to clinical applications applying expertise of other team members.

Conclusion

- **Strengths and opportunities:**

- The link with ENVA and access to large animal model facilities is a unique strength.

- The team gathers interdisciplinarity and large spectrum of expertises allowing to easily recruit talentous students.

- There is a large capacity to supervise students with 18 researchers holding HDR.

- The fund raising was efficient.

- The team has active collaborations with renowned researchers in the field.

- **Weaknesses and threats:**

- A high proportion of teacher-researchers have heavy teaching duties.

- At the moment, a part of team members are dispersed into different geographical locations, which may negatively influence planned interactions.

- There are complex ethical issues concerning using large animal models.

- **Recommendations:**

- Regular contacts between members of this large team will be critical for implementation of successful common projects.

- Number of targeted NMDs appears very large and a prioritization of one or two of them would help in developing specificity/research identity of the team.

- Attracting postdoctoral fellows can be improved considering team as a whole.

Team 8: Genetic psychiatry

Name of team leader: Ms Marion LEBOYER

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	3	4
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)	12	9
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	4
N6: Other contractual staff (without research duties)	3	3
TOTAL N1 to N6	**21**	**21**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	3	

• Detailed assessments

Assessment of scientific quality and outputs

The team develops from a psychiatric genetics laboratory, which has progressively expanded its focus to study the pathophysiology of underlying mental disorders. The scientific quality of the team is unquestionable. The number and quality of the publications produced by the team is enormous. During the period 2008-2013, they have published 196 international and national papers including, among others, 2 Nature, 3 Nature Genetics, 1 Nature Medicine, 3 Lancet and 11 Molecular Psychiatry.

They are clearly key leaders in their field of knowledge. This can be also appreciated by the different recognitions and prizes that team members have received. However this field appears to be restricted to genetics. Many of the publications outside this field are collaborations.

It is also important to notice that different members of the team participate in editorial boards of prestigious journals. Recent data they obtained are organized on 6 different research lines (early onset bipolar disorder, immunogenetics, circadian genes, emotional hyper-reactivity, genetic analysis of autism spectrum disorders (ASD) and identification of environmental susceptibility factors). Each of these research lines is well supported by recently published data in high impact factor journals such as Lancet, Nature, Nature Genetics, Nature Medicine or PNAS. Some of the research lines are especially novel and all of them are highly translational. The research of the team to date has provided a solid ground on which to expand their knowledge on the genetics of psychiatric disorders to a wider understanding of these diseases, including their neurobiological basis, their diagnostic or their treatment. However, they seem to have done very small work outside genetics until now.

Assessment of the unit's academic reputation and appeal

This team has an outstanding academic reputation and appeal. They have been responsible of the creation of a private scientific foundation, which goal is to coordinate all national researches on basic and clinical psychiatry. They also participate in different national multicentre projects focused on psychiatric research, both at the clinical (cohort studies) and the basic levels. The LABEX-BioPsy is an excellent initiative. They have received funding for multiple national and international research projects, including some from FP7. Their network of international collaborations is also impressive. The recent arrival of a new member will reinforce their attractiveness. The organization of different national and international meetings and the participation of members of the team in different councils of scientific societies also reinforce the reputation and attractiveness of the team. They have been able to recruit new staff on a regular basis during the last years and some of their personal, especially graduate students and postdoctoral fellows have found new and attractive jobs after leaving the group.

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

The team has participated on the estimation of the economical burden of psychiatric disorders in France, a very important type of study to inform both politicians and the public of the importance of psychiatric research and to impulse its funding. The team has also been involved in different projects directed to disseminate the important impact of psychiatric disorders in our society, not only at the economic level, and the necessity of increasing the research on this matter. Some of these projects have involved direct contact with general public and mass media. Additionally, they also promote these interactions through the Fundamental Foundation. In summary, the team 's interaction with the social and cultural environment is impressive. However, the interaction with non-academic partners and the knowledge transfer is still incipient and should be promoted.

Assesment of the unit's organisation and life

The expertise of each of the team members is not clear and this is important since some projects involve very different experimental approaches and the committee could not identify whether they could be performed by members or through collaborations. A plan for coordination with other structures in ESPRY (some meetings with other teams involved in related research should be desirable) is lacking.

Assessment of the unit's involvement in training through research

The team has demonstrated in the recent years that it has been heavily involved in Master and PhD training, participating in juries and teaching in master and graduate programs. Several members (5) of the team are qualified for supervising research. Since 2008, the team has trained 5 PhD students, 4 have defended their thesis and have continued to do clinical research within a senior position of psychiatrist, 1 is doing a post-doc in the US and 1 has obtained a position in Industry. There are 4 graduate students with on going thesis in the team. Apparently, the integration of doctors in the job market has been extremely succesful. The team has developed a scientific retreat (once a year) to have presentations from graduate students and postdoctoral fellows. It also has promoted, through LABEX BioPsy a similar experience.

Assessment of the five-year plan and strategy

A four-year strategy is well planned and organized in 5 transversal programs, each of them coordinated by different PIs. These programs are based on solid evidence obtained by the group in the former contract and are already well funded for this time period. The different programs are very innovative and fit some of the most novel research strategies for psychiatric disorders. The two main objectives for this period seem to expand research from a mostly genetic perspective into one that takes into account the interaction with the environment and other that deepens into the etiopathology of psychiatric disorders. One concern is that only the program on synaptic vesicle genes seems to explore the neurobiological bases. It would be extremely interesting to consider the development/use of animal models or other research tools for this purpose in other programs, especially in that related to immunoinflammation. The team does not foresee any change in the strategic direction of their research and, consequently, no alternative paths are described.

Conclusion

- **Strengths and opportunities:**

- The team has a long term expertise in psychiatric research, especially in genetics.

- There is a solid network of collaborations with different national and international research groups and institutions.

- Secured funding has been obtained for most of the projects planned.

- There is a high number of research supervisors in the team.

- The technical support is covered through interaction with Fundamental Foundation, a private research foundation directed by the team leader, which aims at boosting French Psychiatry research on major mental disorders by coordinating the activities of its clinical and basic research teams.

- Clear, innovative and solidly based research lines are proposed.

- The team has an active involvement on the advocacy for the investment on research in psychiatric disorders.

- The team has demonstrated capacity of research training.

- There are opportunities of expansion and further collaborations through the expected fusion of Universities and through LABEX BioPsy.

- There is a possibility of use of powerful research tools, such as the Fundamental Cohort.

- **Weaknesses and threats:**

- Since the 5 different lines of research planned are very different, it is possible that they progress “too independently”. A minimum overlap between the different lines is desirable.

- Some of the research lines do not have yet a plan directed to understand better the etiopathology of the disorders studied. This should be constructed in each case, at least as a long term objective.

- **Recommendations:**

- The team has to build plans directed to understand better the etiopathology of the disorders studied, at least as a long term objective. To date this is only performed in the research line focused in synaptic vesicle genes.

- The team has not provided a detailed account of the structure, organization and individual expertise of the team members.

- The team should make a significant effort, especially in incorporating researchers specialized in basic neurobiology, to expand their own research outside the field of genetics.

Team 9:

Restorative Neurosurgery using Biotherapies and Advanced Technologies in Neurology and Psychiatric disorders

Name of team leader:

Mr Stéphane PALFI

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		1
N2: Permanent EPST or EPIC researchers and similar positions		
N3: Other permanent staff (without research duties)		4
N4: Other professors (PREM, ECC, etc.)		2
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6		**8**

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

• Detailed assessments

Assessment of scientific quality and outputs

This is a new team that focuses on clinical research in the domain of functional neurosurgery of neurodegenerative diseases in Humans especially Parkinson's disease (PD) and Huntington's disease (HD). This team is clearly very different fron the standard model in neuroscience as it involves "only" neurosurgeons (with clinical duties at Henri-Mondor Hospital), apart from one research engineer and one post-doctoral researcher, with long-established collaboration with closely related laboratories of neurobiology that have developed animal models (murine and non-human primates), (CEA, MIRCEN). This collaboration typical of translational research from development of model and concepts in animal models to clinical application, consists in the past few years in the development of gene therapy using non replicable lentivirus and optogenetic tools to restore and modulate neural activity in disease-specific brain targets. The research is therefore especially innovative; it stands as a world-class example of neurosurgery team that has almost unique expertise in the domain of bio-therapies and functional neurosurgery. It allows team members to develop on-going clinical trials, in PD patients for instance.

Recent publications of the team members demonstrate the feasibility of these new treatments and their potential therapeutic efficiency in patient populations. Examples of these studies are the application of a lentiviral vector-based gene therapy for Parkinson's disease in humans (Lancet 2014) or the use of thalamic stimulation to improve fraglil-x associated tremor (Mov. Disorders, 2012) Other publications in good to highly visible international journals were also produced by the team mainly as co-authors (J Neurobiol, Neurol Neurochir Pol, Neuroimage, Eur J Pain,...)..

Assessment of the unit's academic reputation and appeal

The unit has an excellent reputation that is undoubtedly reinforced by its relationships with a large amd long-established network of collaborations in both the clinical and the neuroscience domain. The team is heavily connected to academic programs for training young neurosurgeons in functional neurosurgery techniques. Formally, there is only one post-doctoral fellow in the team but this should might improve in the future depending on the development of cutting-edge, innovative clinical trials.

The team has proved high capability for fund raising as it benefits from a number of grants over the past decade and currently, of either industrial (Industrial Oxford Biomedica), public or charity origins, in which the team PI is either co-applicant or main applicant.

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

Involvement in several communication activities towards various media, participation in radio programs is effective. General audience conferences were given (eg . Cité des Sciences La Villette).The team has links with patient associations.

Assesment of the unit's organisation and life

This is a clinically oriented unit with strong specificities relating to patient assessment and care. This is a small and well integrated team and as such there is no particular need of excessive regular meetings. However, more information on the organization and the day-to-day functioning of the team was not clarified during the visit. The team should develop a web page to coordinate/make public their research. A plan for coordination with other structures in ESPRY (some meetings with other teams involved in related research should be desirable) is lacking.

Assessment of the unit's involvement in training through research

The team leader participates in Master (especially two new M2 programs connected to neurosurgery) and Doctorate courses. Two PhD students have been recruted during the period evaluated and are conducting their thesis in the team. Although the previous experience of the team in training is reduced, they acknowledge the existence of a postdoctoral research training program with a Japanese University, which has to be formalized.

Assessment of the five-year plan and strategy

The research strategy is directly in line with the previous activites and with very recent publications that demonstrated the major interest of gene therapy in Parkinson's disease. It will also relate to the strong interactions with other teams of the Centre in the domain of psychiatry (Team 8), neuropsychology (Team 6) and operations (The new one which will join in 2016). The scientific strategy for 2015-19 period is organized into 3 main research lines including 1/ gene and cell therapy for neurodegenerative disorders, 2/ electrical and optical neuromodulation for neuro-psychiatric disorders and 3/clinical development of neurosurgical tools. Each of these research lines is solidly supported by previous results and appears to be in advanced stage of development. Although the unit has ongoing collaborations with both external and internal teams to develop these projects, the hiring of new engineers and postdoctoral fellows is necessary to be able to reach this wide task. Some of the new incorporations are planned in the report.

Conclusion

- **Strengths and opportunities:**

The team offers as an impressive example of highly successful translational research in which a neurosurgery team develops cutting-edge innovations thanks to its long-established collaboration with neuroscience laboratories.

- **Weaknesses and threats:**

The team lacks permanent research-dedicated staff such as those from University or research Institutes (eg. INSERM, CNRS, …) . This might not be a real problem since the strong interactions, already established with other groups provide the team with scientific input and interactions.

- **Recommendations:**

The team will greatly contribute to the current Centre proposal in its neuroscience component, mainly through its expertise on neurosurgery and gene and cell therapy. However, in order to do so, they shoud develop a detailed plan for increasing the number of staff, specially postdoctoral fellows, graduate students and technical staff.

Team 10: Peripheral and central nerve excitability and therapeutics

Name of team leader: Mr Jean-Pascal LEFAUCHEUR

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	5	4
N2: Permanent EPST or EPIC researchers and similar positions		
N3: Other permanent staff (without research duties)	4	4
N4: Other professors (PREM, ECC, etc.)	4	3
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**13**	**11**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	5	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	

• Detailed assessments

Assessment of scientific quality and outputs

The results of studies conducted by the team can be summarized as follows : 1/ Better characterization of neurophysiological markers of small fiber neuropathies (measure of thermal and pain sensations by quantitative sensory testing and evoked potentials), 2 /Implementation of repetitive transcranial stimulation to treat neuropathic pain (as well as epidural motor cortex stimulation), 3/ Investigation of cortical excitability to assess exercise induced fatigability in multiple sclerosis, 4/ Development of neurophysiological biomarkers of peripheral neuropathies and multiple sclerosis, 5/ Development of an image guided navigation strategies to optimize optimize trancscranial magnetic stimulation (TMS) and motor cortex mapping.

The expertise of the team in mastering the TMS and motor cortex stimulation techniques is impressive. The output of studies dedicated to the treatment of neuropathic pain and sensory motor neuropathies seems particularly robust and relevant. The neurophysiological testing of small fiber neuropathies has been as well quite appropriately developed. Nevertheless, information and precisions are missing to better understand in which respect the neurophysiological parameters registred have all the characteristics of biomarkers (validity, specificity etc..). The relationships between the neurophysiological characteristics which are collected by the team members and the possible mechanisms underlying the development of this pathology are not explicited neither. It seems that the members of the team are more involved in the clinical and therapeutic implications of their domain of expertise than into the in depth exploration of the pathophysiology or of the basic mechanisms which are at the origin of the disorders they are exploring. The main publications are reflecting this orientation. The list of publications in the 5 last years is impressive but most of the articles have been published in medium ranked journals except one for which the PI is first author in 2009 (Brain) and another one for which he is last author in 2011 (Nature Neurol.). The expertise of the PI for image guided brain navigation in TMS practice is generally well recognized.

As a conclusion there is absolutely no doubt about the expertise of the team, the data provided are of a very good quality but the pure research component is more limited than the clinical technical or therapeutic aspects.

Assessment of the team's academic reputation and attractivity

The team leader has been invited in numerous international conferences and is recognized as one of the most reknowned experts in the domain of rTMS. He is as well recognized as one of the best experts in term of image guided navigation in TMS and is participating in many consensus committees for SFNP, EFNS. One other PI is the founder of a network specializing in inflammatory disease in Ile de France.

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

One patent has been registered by the team and another one is in progress. Collaborations with the pharmaceutical industry are important (Cephalon, GSK, Sanofi, Merck etc…). The team has participated in pain research forum and has given interviews to the media in this domain. Implication in social events is reported as well.

Assesment of the unit's organisation and life

The team appears to be organized both as a clinical research team and as a provider of different techniques for the hospital and for external collaborations. As mentioned previously, a full time researcher is perhaps missing to ensure complementary research driven "priority" orientations to the team. The implication of some members of the team in research seems to be quite fragmented. Strategic meetings are held every 6 weeks but more research and administrative support is probably needed.

Assessment of the team involvement in training through research

The unit's involvement in training through research is extremely good. 4 PhD students have defended their theses since 2009, each of them publishing 4 papers, one is ongoing. All the PhD students have obtained a permanent position afterwards. Similarly, 5 post-doctorants from a large variety of countries have joined this laboratory during the same period. The team leader is member of the scientific committee of the "Ecole Doctorale SVS" of the Creteil University and the majority of the team members are involved in the different neurosciences oriented courses of the University (university diploma, masters, including a master 2 focuses on the motor system).

Assessment of the five-year plan and strategy

The five year plan is based on three leading projects which are 1/ the characterization and treatment of painful peripheral neuropathies, 2/ the characterization of excitability disorders supporting the development of fatigability in inflammatory demyelinating diseases, and 3/ the characterization of cortical excitability and plasticity changes related to motor disturbances in the context of multiple sclerosis and motor stroke. To achieve these goals, the team will be divided into two subgroups: the first one in charge of the exploration of peripheral neuropathies, the second one in charge of demyelinating diseases and stroke. International collaborations and collaborations with local and national teams are foreseen for these projects. The first 2 projects are the continuation of ongoing studies with a different share of the workload between the two main subgroups (which in this repartition will differentially subspecialize). Research for biomarkers is still the priority of the team together with a more in depth genetic characterization of the neuropathies. Not so many details are provided regarding this axis besides the collaboration with geneticists. The third project – motor stroke -corresponds to a rather new domain of exploration (at least in its therapeutic implication). One can notice that besides the mention of the plasticity induced by cortical stimulation, the physio-pathologic rationale for such strategy is not explicited and remains rather vague.

In summary the clinical, technical and therapeutic implications of this research plan are very good but from what is exposed by the team leader, no major breakthrough can be expected and the mechanistic approach of the research on stroke for example remains a little bit limited.

Conclusion

- **Strengths and opportunities:**

- There is a very good access to clinical recruitment through the hospital, networks and collaborations.

- The team has an excellent technical and theoretical expertise in the area of brain stimulation and of image guided brain navigation.

- Complementary techniques have been developed for studying neuropathic pain.

- The leader has a high international reputation.

- Significant therapeutic achievements have been obtained.

- The team will benefit from the restructuration of neurosciences research at IMRB and from collaborations with the ESPRY department.

- The team has developed new international collaborations.

- **Weaknesses and threats:**

- The team is lacking at least one full time researcher, since the team leader is the most “permanent” researcher and he has many other duties

- The team is too small to accomplish all the objectives listed. New recruitments are planned, which are absolutely necessary to develop the projects. Otherwise, most of the work should be organized in collaboration with other groups (especially that concerning basic research).

- There is a lack of visibility of a truly “research driven” axis and clinical studies seem to be the main activity. No exploration in depth of mechanisms is achieved.

- The stroke axis is not well documented.

- Funding of the team seems to be limited.

- Lack of administrative support may lead to work overload, specially on PIs.

- Interaction with biotech companies is still incipient.

- **Recommendations:**

- The productivity and the activity of the team rely too much on the sole activity of its leader.

- Recruitment of a more permanent researcher, as well as administrative and technical support personnel seems to be mandatory.

- Better explicited models for the exploration of the diseases have to be proposed.

Team 11: Pathophysiology and pharmacology of coronary disease and cardiac failure

Name of team leader: Mr Bijan GHALEH

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	12	11
N2: Permanent EPST or EPIC researchers and similar positions	4	3
N3: Other permanent staff (without research duties)	5	4
N4: Other professors (PREM, ECC, etc.)	1	2
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	1
N6: Other contractual staff (without research duties)	2	
TOTAL N1 to N6	**28**	**21**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	10	
Theses defended	8	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	11	

• Detailed assessments

Assessment of scientific quality and outputs

The team currently directed by A. Berdeaux will be reorganized (one group will leave) and the director of the team will change. This is a large team of about 40 persons with 11 HDR (professors, clinicians, researchers) with important number of young researchers. This team is subdivided in 5 subgroups with one of them that will not be part of the team in the next period. The scientific production in general is excellent. During 2008-2013, 78 articles were published in which the members of the team are major contributors: 3 with IF>15 (Circulation), 2 with 15>IF>10 (Eur Heart J), 27 with 10>IF> 5 (Basic Res Cardiol, Cardiovasc Res, FASEB J…) and 18 with 5>IF>3.5 (Am J Physiol, J Pharmacol Exp Ther, Br J Pharmacol…). Moreover, members of the team also participated in 55 other publications not directly related to the team project. In addition, 24 other publications with IF<3.5 are issued from clinical veterinary research. The major findings in the 2008-2013 period concern: i) the use of hypothermia by total liquid ventilation during myocardial ischemia and cardiac arrest and ii) the identification of AngPTL4 as a potent protein protecting against the no-reflow phenomenon during myocardial infarction. There is an important scientific potential and link with Veterinary School Maison Alfort providing unique opportunity for using large model animals including DMD dogs. Link with clinicians, which are either part of the team or external collaborators is also of interest, in particular with respect to planned evaluation of pharmacological cardio-protective strategies. The strong interaction with clinicians allowed the design and/or the participation to four clinical trials in the field of acute myocardial infarction.

Assessment of the unit's academic reputation and appeal

Team members participated in the organization of 3 national and 1 international meetings in the field of cardiology. They contributed to EU MITOCARE program being leaders for 2 work packages. They established several international (Canada, U.S.A., Italy, UK) and national collaborations that allowed the publications of various joint articles. The team has an impressive success rate in national fund rising (9 ANR grants during the 2008-2013 period) and the members of the team obtained several grants from national research associations (FRM, AFM, Fondation of France, Fondation de l'Avenir, SFHTA) indicating attractiveness of performed work. Team members gave 30 invited talks at national and international conferences. They are reviewers of several international journals and are members of national and international scientific committees.

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

Team members established several collaborations for R&D programs with pharma companies such as Trophos, Echosense and Servier. 2 patents have been registered. Findings concerning hypothermia, total liquid ventilation and protective strategies to cardiac arrest have been largely commented in newspapers and TV/radio programs.

Assessment of the unit's involvement in training through research

Large number of PhD students (18 with 8 defences) and master 2 students (14) have been trained during the last 5 years. Team members are also highly involved in teaching including 2 different M2 modules and several M1 and diploma modules. The former team director, is also directing the Doctoral School “Health and Life Science (Univ.Paris Est).

Assessment of the five-year plan and strategy

Scientific strategy appears well balanced and designed to further exploit strengths of the team. Like for the period 2008-2013, the project will take advantage of the strong interaction with the Veterinary School Maison Alfort and will involve several clinicians. This strategy is a major advantage in view of the translation of basic results to the clinic.

The main objective of the project is to protect the heart, to reduce infarct size and to prevent acute and chronic left ventricular (LV) dysfunction. The part of the project concerning the prevention of acute cardiac damage will be focused on the role of mitochondrial cholesterol translocation and oxidation in ischemia-reperfusion injury. This part of the project is particulalry innovative and interesting. Based on the results previously obtained by the team, alternative cardioprotective strategies will be also investigated, in particular the protection of the coronary vascular network by the administration of previously identified ANGPTL4 that improves myocardial perfusion.

A second objective consists in the prevention of LV dysfunction occurring after cardiac arrest and in heart failure with preserved ejection fraction (HFpEF). The work on prevention of acute LV dysfunction after cardiac arrest is the continuation of the innovative results previously obtained by the team and will focus on the benefits and protective mechanisms of hypothermic total liquid ventilation. Of note, collaboration with private company is ongoing to develop specific total liquid ventilators and their use in clinic. Concerning chronic heart failure, the team will investigate the role of altered intracellular calcium handling (in particular in relation to ryanodine channels) in HFpEF. This project will be performed on an original pig model of HFpEF designed by the team. The model of HFpEF in a large animal is particularly interesting as it allows the detailed analysis of the functional and morphological cardiac abnormalities in this still controversal form of heart failure.

Conclusion

- **Strengths and opportunities:**

- The team is recognized for its expertise in cardioprotection.

- The team has access to large animal models.

- There is a real translation to the clinic.

- Collaborations with pharma companies are effective.

- There are strong student training activities and large number of researchers with HDR.

- **Weaknesses and threats:**

- The team is located in two separate places implying that daily contact between team members is difficult.

- The team has a weak expertise in molecular biology.

- **Recommendations:**

- There is a need to increase the number of team meetings to improve cohesion within the team.

- The team might exploit its potential of interactions with private companies.

- Policy to recruit scientists with strong skills in molecular biology and cell biology has to be envisioned.

Team 12:

Pathophysiology of COPD and other respiratory consequences of environmental particles inhalation

Name of team leader:

Mr Jorge BOCZKOWSKI and Ms Sophie LANONE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	9	9
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)	3	3
N4: Other professors (PREM, ECC, etc.)	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	2
N6: Other contractual staff (without research duties)	1	1
TOTAL N1 to N6	**17**	**18**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	8	
Theses defended	9	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	8	

• Detailed assessments

Assessment of scientific quality and outputs

The team leader's research activity has long been devoted to pathophysiology of Chronic Obstructive Pulmonary Disease (COPD) and he is probably a pioneer in the field of this major public health issue. This team is still one of the few interested in COPD. It has developped a translational approach of the disease by developping relevant animal models and studying human tissues.

Since 2009, the team has evolved in two complementary axis, the first one being specifically related to COPD, and the second on the respiratory effects of environmental particles inhalation. This second axis addresses the problematic of occupational pollution but has focused in the last years on nanoparticles, either naturally contained in environment, or manufactured and industrially designed.

By studying the pathophysiology of COPD in the one hand and the effect of nanoparticles on lungs on the other hand, this team is unique.

The COPD axis comprises three scientific developments: the role of oxIdative stress in COPD with works on heme oxygenase and on NO; cellular senescence and COPD with a focus on the role of prostaglandins in this process and on the importance of the Th17/Treg balance; the genetic origin of alveolar growth disorders. This last axis developped by a pediatrician more recently integrated in the team, seems difficult to be related to COPD but it is interestingly hypothesized that early origins of COPD could relate to lung development.

Overall to comment these three parts of the COPD axis, the committee thinks that the first one is in the linear continuation of previous works of the team and appears as a logical development but the two others are very original and innovative. Senescence relie new thematic on senescence in respiratory and other chonic disease with very innovative results in COPD. The third one is completely different since it concerns genetics, a new approach in the team, lung development, a probably crucial process for pulmonary diseases occuring later, and pulmonary diseases of the premature neonates, a series of diseases not studied before in the team. The team has developed animal models of COPD in smoking mice and also models of exposure to pollutants that are inestimable tools for their research strategy. This team is unique in France in possessing such models.

In turn the environmental particles axis is presented as 3 sub axis: the first one relies on asbestos exposure and relationships with obstruction, mesothelioma and pleural plaques using a large cohort of exposed retired workers; the two others relie on nanoparticles: toxicity of carbon nanotubes, and metal oxide nanoparticles. The effect of titanium dioxide was investigated on cultures of fibroblasts, in animal models and in humans.

The scientific production is regular and of first rank. Indeed since 2008 73 papers were published (of which 29 as first or last author), among which 9 with IF > 10 and 12 with IF between 7 and 10. The team has published in Am J Pathol, FASEB J, Mol Carcinog, Thorax, Am J Resp Crit Care Med, Physiol Genom, Lab Invest, Am J Resp Cell Mol Biol, Exp Lung Res, Part Fibre Toxicol,...

Assessment of the unit's academic reputation and appeal

The team participates to several networks including Helmoltz – INSERM collaboration, 2 PIA objects dealing with nanotoxicity, an Equipex NanoID and Labex Serenade and participation to the national programs on mesothelioma.

Team leaders are sollicitated as experts in various instances and for research projects. They are also involved in the organization of national and international meetings.

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

Several participations to whole public and TV conferences and debates have to be mentioned.The team has developped two industrial collaborations (Arkema, Harmonic Pharma) and has three patents.

The team is participating to the DHU devoted to pulmonary and cardiovascular pathology but also Ageing in the frame of which a fondation was created.

Assessment of the unit's organisation and life

The team is clearly organized around basic and translational approaches in a medical school, hospital and animal facilities environment guarantying all the feasibility of the projects developped. The team is organized as two main subgroups, COPD and nanoparticles, the first one being in turn divided in two axis, namely cellular senescence and early origins. Regarding scientific animation, three regular meetings (2 weekly, 1 monthly) are organized, plus a one day seminar once a year. Regular participation to various national (J2R) and international meetings is effective.

Assessment of the unit's involvement in training through research

The team is implicated into 2 masters, the team leader being responsible for the training Campus of the DHU Ageing Thorax Vessels Blood, and one team leader being involved in the Education programm of the Labex Serenade.

8 members of the team have HDR. A large number of PhD students (17 with 9 defences) have been trained during the last 5 years period.

Assessment of the strategy and the five-year plan

The project is presented as being developped in three parts: senescence and COPD, environmental particles, and early origins of COPD and other consequences of exposure to environmental particles.

In the first axis, it is proposed to continue 3 sets of STUDIES, which are the relationships between senescence studied through the P53 P16 and telomerase reads out and the developement of COPD, the role of PGE2, and systemic aspects of senescence and COPD. The P53 expression will be studied in macrophages and type 2 pneumocytes. P53 KO and conditional KO for P53 in P2 will be challenged in the COPD model. A similar approach will be developed for P16 and telomerase. The role of PGE2 will be investigated using mice KO for the PGE2 receptors. The role of sPLA2 (which induces PGE2) will be studied in COPD fibroblasts. Also, the role of PGE2 on the induction of Th17 cells will be investigated. miRNA 146a and DNA methylation will be studied as regulators of COX2 expression in fibroblasts. The plasticity of these cells regarding their capacity of reprogrammation in COPD will be assessed. Regarding systemic senescence, various parameters will be checked in COPD mice.

In the second axis, a series of human studies is proposed with (1) further studies on the cohort of workers exposed to asbestosis; (2) a comparison between occupational and tobacco-induced COPD. The hypothesis of a defect of autophagy capacities altered by carbon nanotubules and nanoparticles is proposed as a potential mechanism of toxicity. For this purpose, macrophages, fibroblasts and epithelial cells will be tested for their autophagic capacities after exposure to nanoparticles in vivo. A translational part will concern painters for whom lung tissues are available. In the frame of the Serenade labex, a series of nanoparticles will be tested in vitro and in vivo for their toxicity.

A third axis dealing with lung development is clearly presented apart. The relationships between maternal smoking and susceptibility to COPD will be studied in vivo in mice. A translational prolongation is proposed in the frame of a collaboration to detect relationships between maternal smoking and markers of senescence. Congenital Cystic Adenomatoid malformations biobank will be studied by omics and the genes of interest will be tested for their dysregulation in COPD. SPOCK2 will be studied in COPD given its importance in brochopulmonary dysplasia.

The project is ambitious, coherent and innovative, with interesting models of COPD in mice and with regard to the study of nanoparticles.

Conclusion

- The team and its project are excellent with a very innovative strategy of development.

- **Strengths and opportunities:**

- The team has a clear leadership in the field of COPD and has recently extended its research to the relationships between nanoparticles and respiratory diseases, which is becoming a very hot topic.

- The projects dealing with the relationships with between pollution and senescence are also very interesting and innovative; ongoing collaborations with team 13 on this topic will doubtless bring added value to this kind of research.

- **Weaknesses and threats:**

- The only significant question is about the position of one of the two team-leaders who will have to quickly qualify as a research director (DR2) to help her developping her leadership in the field of nanoparticles-inducing respiratory diseases.

Team 13 : Role of cell senescence in pulmonary and cardiovascular diseases

Name of team leader: Mr Serge ADNOT

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	3	6
N2: Permanent EPST or EPIC researchers and similar positions	1	
N3: Other permanent staff (without research duties)	3	2
N4: Other professors (PREM, ECC, etc.)	2	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	5	3
N6: Other contractual staff (without research duties)	3	2
TOTAL N1 to N6	**17**	**14**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	6	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	5	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	4	

• Detailed assessments

Assessment of scientific quality and outputs

The team has historically developed an unique and well recognized expertise in the field of pulmonary hypertension (PH) with a basic and a translational approach in idiopathic PH but mainly in secondary PH, allowing an interest to a large panel of respiratory diseases. This team has developed a panel of new therapeutic targets in the field. Since 2009 and the beginning of the present contract, this team has developed the concept of senescence as a general mechanism of inflammatory and remodelling diseases, and has developed this axis not only in the field of PH but also in other respiratory diseases. This very original approach allowed the team to get an outstanding leadership in the field.

Accordingly the work accomplished since 2009 gathers first rate publications in the field of PH: they identified extracellular mediators and intracellular signals involved in smooth muscle cells (SMC) from pulmonary arteries including 5-HT. Transgenic mice overexpressing 5-HT transporter in SMC allowed the team developing a model of spontaneous PH, and deciphering the mechanisms of it and proposing 5-HT as a therapeutic target with promising inhibitors. This series of works led to 8 publications (J Clin Invest, 2009, Circulation, 2010, ASEB J, 2009, Am J Resp Cell Mol Biol, 2013, Am J Physiol, 2012, Am J Resp Crit Care Med, 2009 and 2011, Chest, 2010). A second series of works in the field of PH focused on secondary PH and acute PH of sickle cell disease, with results relying to the vascular dysfunction and to the damage of mechanic ventilation in the context. Some additional clinical works on right heart dysfunction in the context of PH led to 9 papers (Am J Cardiol, 2013, J Card Fail, 2012, Circul J, 2012, N Engl J Med, 2011...).

Regarding the senescent cell axis, studies since 2009 started from PH secondary to COPD with the evidence of PA-SMC senescence being a mechanism of PH (Circulation, 2010, Cir Res, 2011, Am J Respir Crit Care Med, 2011,...). This very innovative axis was developed for a part in collaboration with team 12. These works extended the concept of accelerated tissue senescence to other cells than SMC in the context of COPD. Subsequent works focused on therapeutic strategies related to senescence, with the inhibition of th P53 – p21 axis by nutlins, showing to induce SMC senescence and therefore decrease PH (1 paper in Circulation, 2013, 1 patent). Other works focused on HIV-related PH and demonstrated promising effects of CCR5 inhibitors (patent deposed on for CCR5 inhibitors as PH treatment). Overall the scientific activity of the team during the 2009 – 2013 period is excellent, with clear paradigm shift, new concept and new investigation proposals.

Assessment of the unit's academic reputation and appeal

The scientific excellence of the team allowed the implication of team members in several international instances and networks such as organizing committee of Am Thor Society and Eur Cardiol Society conferences (PH and cell senescence groups), European network of excellence on cell senescence. The team participated to several FP7 and other European initiatives.

The attractivity of the team is well illustrated by the presence of 2 post-doctoral fellows co-granted by Helmoltz and INSERM, 2 foreign invited professors, and the recruitment of 3 senior researchers.

Several awards were obtained by members of the team including the Prix de l'Académie de Médecine and Prix Jeanne-Philippe Beziat (FRM).

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

Three patents were deposited during the term and a 4th is under evaluation. Several partnerships with industrial companies are developed.

Importantly, the team leader coordinates a DHU devoted to pulmonary and cardiovascular pathology but also ageing in the frame of which a fondation was created.

Assessment of the unit's organisation and life

The team is clearly organized around basic and translational approaches in a medical school, hospital and animal facilities environment guarantying all the feasibility of the projects developped. The team is rather small and does not comprise any full time researcher which is identified as a relative weakness.

It comprises 8 physicians, 5 technical staff, 3 post doctoral fellows and 6 PhD students. All platforms including animal facilities, flow cytometry, omics and function (cardiac and respiratory) assessment are present and shared by the different teams.

Regarding scientific animation, every student presents his work every week and students are involved in several meetings in France and abroad.

Several animal models are developed or obtained through fruitful collaborations. Several cohorts of patients are accessible either locally or also in the frame of collaborations.

The presence of a DHU facilitates the development of translational works and of the clinic/research interface.

Assessment of the unit's involvement in training through research

The team leader is responsible for one M1 and M1/M2 sequence is being proposed around the thematic of ageing. The researchers of the team have all some teaching activities through their university valence. For each PhD student, a tutor is following the work, with intermediate evaluations of the thesis every year. 5 PhD have been defended during the period 2009-2013 and 6 are ongoing.

Assessment of the strategy and the five-year plan

The project is focused on 1/ the study of the molecular mechanisms responsible of lung-vessel remodelling in PH and 2/ the role of cellular senescence in pathogenesis of chronic lung and cardiovascular diseases. These two research axes will include molecular approaches in vitro, validation of the results in different models of wild type and genetically modified animals and the translation to the clinic. Based on the previous research activity of the team, its ability to transfer basic results to the clinic and the recent results obtained in the field of cell senescence, the project seems to be fully feasible.

The first axis presented is divided in 4 parts. These parts are complementary and cover all the aspects of PH pathophysiology in a translational strategy:

- A basic part using transgenic mice designed to conditionally express some signalling molecules in PA-SMC. The approach is logical and represents an innovative development of what was done before.

- A second part focused on inflammatory mechanisms around PH, with a set of experiments related to chemokines and chemokine receptors, mainly fractalkine and its receptor; a second set of experiments concerns the importance of CCR5 in the context of VIH infection. The role of calpain/calpastatin and of IL1-ß will be also explored using specifically designed transgenic mice.

- Therapeutic intervention targeting senescence in PH. Again several sets of experiments are proposed. In the logical continuity of previous works on nutlins, the effect of these potential drugs will be studied in terms of mechanisms involved. Also the role of telomerase and p21 will be investigated. Lastly, a model of sickle cell disease will be investigated in collaboration with other labs.

- A series of clinical projects in the field of congestive heart failure and the associated PH, COPD, cystic fibrosis and SCD. This axis appears as coherent with the past activity. It is well described. Many collaborations are apparent. The feasibility of the project is certain.

The second axis focuses on senescence and is probably more innovative. It is especially important in the context of the expected explosion of chronic diseases prevalence in the next years due to ageing. This axis is clearly beyond PH but also beyond respiratory and cardiovascular diseases and introduces a real breakthrough. It is the core of the DHU coordinated by the team leader. This axis is much more important than the previous with 8 parts: senescence and COPD in mice and men; in CF through the study of cells obtained in transplanted patients; study of senescence / remodeling pathways; mechanisms of senescence induction (oxidative stress, inflammation); anti-senescence therapies; senescence and cardiac remodeling; immune surveillance of senescence; clinical research. In the clinical part, it is proposed to create a unit of functional exploration of ageing. Several studies are proposed, in the canonical diseases explored in the team (CF, COPD, SCD, VIH) but also diabetes, sleep apnea syndrome and cardiac amyloidisis.

These projects appear very ambitious and the proposal of an exploration unit devoted to ageing seems interesting and highly tranversal and innovative.

Conclusion

The team and its project are excellent with a very good and innovative strategy of development.

- **Strengths and opportunities:**

- The strength is to be a clear leader team in the field of PH, and to have taken the opportunity of studying senescence first in the field of PH and then in the whole frame of chronic diseases.

- The team has an excellent expertise in the molecular aspects of lung-vessel remodelling in pulmonary diseases.

- Avalaibility of cohorts patients and different approaches for clinical characterization of patients is a real strength.

- The team has strong competences in translational research.

- **Weaknesses and threats:**

- There is no permanent full time scientist.

- Inter-group integrated research can be reinforced.

Team 14: Biomechanics & Respiratory apparatus: A multi-scale approach

Name of team leader: Mr Bruno LOUIS and Mr Marcel FILOCHE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	6	5
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)	6	6
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**17**	**15**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	11	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	9	

• Detailed assessments

Assessment of scientific quality and outputs

The team members (i.e., currently 11 with PhD) are highly qualified in the fields of respiratory biomechanics and cellular mechanics and much renowned by the relevant international community. The scientific production includes 179 articles (161 original studies and 18 reviews) by the team members and an additional 104 articles by the new members, most of them in journals with relatively high impact factors. The publications are in diverse areas that include medicine, physiology, bioengineering, physics and mathematic (12 publications with an IF >10; 2 publications with an IF >30). In respiratory mechanics, they significantly contributed in the 2 major areas: 1) diagnosis of respiratory failure and advanced treatment with mechanical ventilators (Chest 2009, Crit care Med, 2009-11, Resp Physiol Neurobiol, 2011-12); and 2) airflow and transport phenomena in the pulmonary airways with special focus on the upper airways and nasal cavity, branching networks, thin liquid films and surfactant transport (PNAS, 2008, Int Care Med , 2011, J Fluid Mech , 2011, Resp Physiol Neurobiol, 2013). In cell biomechanics, their major contributions were in the areas of 1) cells mechanical and adhesive properties in response to forces (Biophys J 2009, Cytoskeleton, 2011, J Biomech 2013), 2) vascular endothelium under stress and remodeling (J Appl Physiol 2011, Biomed Mater Eng 2012, Eur Respir J 2013); and 3) dynamics of ciliary beating to improve diagnosis (J Med Genet 2010, Eukaryot Cell 2011, Orph J Rare Dis 2012). Another impressive, as well as unique point, is the span of these scientific activities from applicable research with clinicians and patients up to basic experimental and theoretical projects in the respiratory systems from organ to tissue and cellular levels.

Assessment of the unit's academic reputation and appeal

The leading investigators are highly recognized within the national and international circles of respiratory mechanics. One of these two is among the top leaders of respiratory mechanics for more than two decades. He has been frequently invited to talk in European and International conferences (e.g., CFD in medicine and biology in the Dead Sea, 2012). He is one of the founders of the European Cell Mechanics meetings and has been co-chair of the recent one in 2013. He is a member of the World Council of Biomechanics and a frequent invited speaker in the cell mechanics and respiratory mechanics sessions of the World Congress in Biomechanics. He was also invited to edit articles in special issues on biofluid mechanics (e.g., J. Biomechanics 2013). The second PI is relatively young in the field, but has gained recognition due to his innovative contributions in the area of respiratory fluid mechanics. Recently, he was the recipient of a Fulbright Fellowship that allowed him to conduct a collaborative research on surfactant delivery at the Biomedical Engineering Department of the University of Michigan. He was also invited for oral presentations in international meetings (e.g., CFD in medicine and biology in the Dead Sea, 2012) and the upcoming WCB2014 in Boston. The team has a good level of participation in national projects and in organizing international scientific events. Two team members have been involved in the European REVA network (i.e., critical care) and Labex Bezout, respectively. In addition, they were members of 3 GDRs and participants in 3 ANR and 1 PEPS-CNRS program. The team also participated in the China-France symposium on regenerative medicine in 2011. The team hosted 1 international visitor (US) for 1 month and 1 Chinese student for 8 months.

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

The team members have collaborated with commercial medical companies involved in the field of respiratory devices. They have a 20-year long history of collaboration with medical gas and ventilator companies such as Taema, Air Liquid and Drager, which resulted in 4 CIFRE agreements to support PhD students. They hold 1 long-term contract with industry. The team is also active in efforts with the Federation ANTADIR to improve medical service by enabling medical assistance at home via development of new medical devices. The clinicians take part in the unit’s efforts to further help and educate the society in their niche of activities via clinical networks and national radio and television programs on popular science and medicine. The team has 1 patent. The team has a very high profile in organizing/participating in international scientific conferences, including those with industry. The team is also successful in disseminating science in the media.

Assesment of the unit's organisation and life

The team in its current conformation is composed of 13 permanent (5 professors or assistant professors, 3 EPST researchers, and 5 MD), 1 technician and 1 post doctoral fellow.

Assessment of the unit's involvement in training through research

The team members are heavily involved in education and supervision of graduate students and training of young scientists. During the past 5 years, 13 PhD students and 3 HDR graduated. Currently, the team is guiding 3 doctoral students. The team members teach at the joint university master's degree in Biology and Pathology (MSc at University Paris-Est Creteil and University Paris--Diderot as well as at Engineering school). They were involved in the establishment of the "Institut Supérieur des Biosciences de Paris" (ISBS), which provides training at the frontiers between biology and engineering. They have an agreement to host a Chinese post-MD for an 8-month research intership. Two team members belong to the Medical School Faculty Council.

Assessment of the five-year plan and strategy

The multi-scale approach for the research program for the next 5 years is appropriate and in time. Based on the scientific achievements of the past years, it is natural to pursue the activities across the spectrum from cell mechanics to organ behavior and patient treatment. The proposal to continue the research efforts along the 3 themes of mechanical ventilation, pulmonary biomechanics (i.e., models of airway obstruction and mucociliary clearance), and molecular and cellular biomechanics is logical and will certainly lead to impressive scientific outcome and benefits to the patients suffering from respiratory diseases. The proved scientific experience of the leading members, as well as the state-of-the-art infrastructure (e.g., Atomic Force Microscopy and Magnatic Twisting Cytometry) and the collaborating opportunities, are promising factors for success. At this time, the commitee did not foresee a special weakness that may impose any threat.

Conclusion

- **Strengths and opportunities:**

- This is one of the best respiratory mechanics and cell biomechanics teams in Europe and world wide with a significant scientific production of high quality. This is also a unique team of biomedical engineering experts within France due to absence of formal bioenginering education in France.

- The present huge opportunities in biotechnology and medical devices, as well as the expansion of multidisciplinary studies that merge biology and engineering puts this team in the frontiers of biomedical research. The team also demonstrated a very good level of advanced training (i.e., access to PhD and MSc students).

- **Weaknesses and threats:**

There is a low rate of hiring new staff and not much inter-group integrated research within the IMRB.

- **Recommendations:**

- The team has to increase recruitment of young scientists, in particular, international high-profile scientists.

- The team has to increase internationalization through joint research projects and networks especially within the EU.

- The team has to further stimulate contracts with industry and inter-group collaborations and integrated research projects with other teams.

Team 15:

Molecular and genetic bases of CFTR and surfactant metabolism dysfunctions

Name of team leader:

Ms Pascale FANEN

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	5	4
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)	5	3
N4: Other professors (PREM, ECC, etc.)	1	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	4
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**13**	**12**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	2	

• Detailed assessments

Assessment of scientific quality and outputs

This is a small team, recently emerging from the break-down of a larger group into 3 groups, which is essentially oriented to rare genetic diseases namely CF and surfactant associated disorders (SAD). Regarding CF, the research activity is organized around three axes: 1/ Genetics of CFTR, with works on the more than 1900 mutations of the CFTR gene and an attempt of classifying these according to the clinical phenotype. The current approach concerns the gene expression regulation through splicing profiles according to various mutations; 2/ Characterization of CFTR partners susceptible to modify the CFTR F508del protein function. Recent examples of molecules of interest include CSNS and COMMD1. 3/ Therapeutic targets, a series of works connected to the above ones, with the interest of COMMD1 as an anti-inflammatory agent. Also, works on the anti-inflammatory properties of sulindac vs ibuprofen are promising in reducing IL8 production. Recent data on a molecule able to target ENaC are also undergoing further investigation. Regarding SAD, studies performed essentially concern the screening and identification of relevant mutations in the SP genes. A focus is made on SFTPC, NKX2-1 and ABCA3.

The scientific production is very good. It is important to consider its progression, with 5 papers in 2013 really emanating from the team (members as first authors).

In the 2008-2013 period, the team in its previous organization had 52 papers (of which 22 as first or last author) + 11 reviews. The team in its present conformation signed 22 papers (of which 13 as first or last author) and 3 reviews in journals like Bioch Biophys Acta, Human Mut, Plos Genet, Respir Res, Plos One...

Assessment of the unit's academic reputation and appeal

The team seems to have a high capacity to attract some international researchers (one foreign post-doctoral fellow, from Canada). The group also has several actions and participation in international meetings and scientific boards listed. One team member belongs to the Am Thor Society International Relations committee.

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

The team has an excellent level of dissemination activities jointly with patient's associations relative to the diseases of interest. Also significant activities at the Clinical Research Hospital Program. It has 2 patents. The team is also successful in disseminating science in the media as well as outreach activities with high school students.

Assesment of the unit's organisation and life:

Currently, the team is composed of 8 members including PhD. Some recent recruitments (CR2, technician with expertise on animal models, PUPH) will allow developing new scientific projects.

Assessment of the unit's involvement in training through research

The team is participating in advanced training at UPEC, Paris-Descartes (the team leader is co-director of the Master Biologie Santé and involved at the M2 level). The team leader is member of the Board of PhD programme University Paris Est, Graduate director of the teaching unit of genetics, MSc courses,). The team has supervised 4 PhD and 5 MSc students during the period 2008-2013.Two team members are participating to 2 teaching units of genetics and to several teaching modules in M1 and M2. students.

Assessment of the five-year plan and strategy

In the 2015-2010 period , the team will focus on 4 main axes:

1) Molecular bases of CF, nasal polyposis, and surfactant associated disorders. This axis will explore new mutations into the CFTR gene or related genes, genetics of nasal polyposis, new mutations responsible for surfactant metabolism dysfunction, gene modifications in patients with SFTPC mutations. In this axis, the main novelty is the access to a cohort of nasal polyposis and to epithelial cells allowing some functional studies. It is difficult to see what will be the forces engaged per topic and in particular for the use of new techniques proposed.

2) Pathophysiological bases focussing on effectors and protein complexes regulating CFTR or SFTPC proteins. It proposes to explore the relationships between chloride secretion and inflammation. A transcriptomic approach is proposed with a study of primary epithelial cells. This part is more the rationale of an hypothesis than a project. Among CFTR partners proposed to be explored, ACTN4 will be studied jointly by the team and a post doctoral fellow from McGill (Canada) in epithelial nasal cells and its relationship to inflammation will be deciphered. However, not much is gven to explain how this study will be conducted. Regarding SFTPC, the effect of different mutations on splicing and resulting protein variants will be studied from bronchoalveolar lavage (BAL) RNA, and the importance of the variants will be tested in vitro with an epithelial cell line. Finally for this axis, the relationships between SP-C isoforms and the autophagy pathway will be investigated. It seems that the proposed research is rather heterogeneous with multiple approaches proposed but no evident coherence between them.

3) Development of innovative anti-inflammatory treatments of CF. The work around COMMD1 will be pursued with the help of bronchial epithelial cells overepressing the protein and screened by whole genome microrarrays. Anti-inflammatory drugs will be tested for their properties in the context of CF. It is questionable to use a mouse model in this context.

4) Translational research. It is more a clinical research part proposing the use of nasal epithelial cell culture and ENaC function assessment to an early diagnosis of CF.

Conclusion

- **Strengths and opportunities:**

- The team has a very good publication track record.

- The team has excellent opportunities for advanced training (access to PhD and MSc students).

- The team has excellent opportunities to integrate basic science with clinical research.

- **Weaknesses and threats:**

- The low rate of hiring new staff could represent a threat.

- There is not much inter-group (IMRB) integrated research.

- The team displays a low level of internationalization.

- **Recommendations:**

- The team has to increase recruitment of young scientists, in particular, international high-profile scientists.

- The team has to increase internationalization through joint research projects and networks (EU, namely).

- The team has to increase networking: interactions with clinic environment, industry and with other IMRB teams.

- Overall, although it is not fully clear what is the workforce put in each axis, and what will be the involvement of the team members vs platform members in the experiments proposed, the project seems a bit large and heterogeneous and would probably benefit from an unification of some axes and focusing on the most promising approaches (transcriptomics, proteomics).

Team 16: Morphogenesis and molecular genetics

Name of team leader: Ms Sylvie DUFOUR

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	3	3
N2: Permanent EPST or EPIC researchers and similar positions	4	3
N3: Other permanent staff (without research duties)	3	4
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)	1	4
TOTAL N1 to N6	**11**	**14**

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

• Detailed assessments

Assessment of scientific quality and outputs

This new team is an assembly of 3 previously independent research groups working on various aspects of neural crest development and neural crest disorders (neurocristopathies): it will gather a former member of the team Molecular Genetics and Development at IMRB, the future team leader currently leading a group at Institut Curie, and a PI directing a group at UPMC. Each of the subgroups has its own particular research focus and strengths. Putting together the applied projects focusing on the genetic, molecular and cellular bases of Waardenburg and Mowat Wilson syndromes (which have resulted in a significant number of papers, including publications in high impact journals (J Mol Med, Dev Biol, Hum Mutat, Eur J Hum Genet, PloS One, Am J Hum Genet (IF = 11.2) with the basic science projects of the future team leader) concerning the role of beta1-integrins and Sox10 (e.g. common publication in Dev Biol 2013) appear highly attractive. The publication track record of these two PI during the last period is at a very good level and importantly has recently been on an upward trajectory in terms of numbers of papers per year. The high quality of the work is reflected by papers published in journals such as Am J Hum Genet (IF = 11.2) in 2013 and Development IF = 6.2); J Cell Sci (2009, 2010) (IF = 5.8). In this context, the contribution to the new subgroup (from UPMC), who has a less impressive publication and fund rising record (although last author paper in J Neurosci IF = 6.9 in 2009), has less impact. However, his complementary expertise in embryological techniques such as chick in vivo electroporation represents a useful extension in applied technical approaches and his area of expertise should add value to the group.

Assessment of the unit's academic reputation and appeal

Team members are recognized in their field, in particular the future team leader who has some international exposure (6 invitations to international meetings in last 5 years). One other PI had 2 invitations to international meeting in this period, a figure that should improve as he becomes more established as a principal investigator. Although team members have participated in the organisation of workshops and meetings in their domains, they are not very active at the international level and there is room for improvement here. There is national recognition resulting from team members serving on national scientific committees. The future team leader has organised one national meeting: “3rd workshop on cell adhesions”. The PI from UPMC has organised one national meeting: an EMT meeting, and is a member of the scientific committee of ARC Fondation. Overall, the contribution to international research initiatives and invitations to prestigious international meetings could be improved. However, the group has provided evidence of its appeal by the recruitment of 1 ARC-funded, 1 ANR-funded and 1 INCA_NIH-funded postdoctoral researchers.

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

Not applicable due to basic science research. This young grouping, which focusses on basic science and genetics, has not had, as yet, opportunities to file patents or have interactions/collaborations with private companies.

Assessment of the unit's organisation and life

With the reorganisation of the groups in January 2015, there will be two subgroups “Molecular basis of neurocristopathies”, and “Adhesive and mechanical aspects of NC development” headed by the future team leader. Due to previous experience of working together on shared and complimentary projects there is every indication that this struture will succeed.

Assessment of the unit's involvement in training through research

The team has been, and is, active in this item as demonstrated by the training and defense of 4 PhD thesis, with 5 PhD theses ongoing. Of note, a PhD student supervised who had two first author papers resulting from her work. Also notable is the involvement of one PI in a PhD project analyzing the role of the SDF1/CXCR4 signalling pathway in cardiac neural crest development which was recently published (with the PhD student as first author) in the high quality journal Circulation Research (IF = 11.8). Subgroups within the current team have been involved in the hosting and training of 20 students in M1 and M2 degrees. All project leaders have been involved in teaching Masters degree courses and have participated in Doctoral school committees.

Assessment of the strategy and the five-year plan

The proposed research plans of the subgroups and the PI joining are subdivided into 3 axes which follow up and extend previous and ongoing work. In particular Axes 1 and 2 propose to make use of the already established large neurocristopathy patient cohort and a number of collaborations that are already in place to characterize disease-causing genes in syndromes such as Waardenberg Syndrome (WS) and Mowat Wilson Syndrome (MWS). In addition to the analysis of human samples, they will utilise animal models such as zebrafish Sox10 mutants (in collaboration with UK) to gain insight into the origin of phenotypic variability in WS and MWS. They will investigate interactions between the WS and MWS causing genes during normal and pathological development of the enteric nervous system (ENS) with a particular focus on Sox10, Zeb2 and Itgb1 in the regulation of cell migration and differentiation. Genome wide approaches will be applied in collaboration with the team 7 of IMRB. They will analyze interplay between genes of interest by intercrossing mouse mutants and analyzing the status of ENS development in the single and double mutant offspring. Additional organotypic gut and neurosphere culture methods will be used to help shed light on the cellular and molecular origins of the ENS defects.

An original and somewhat new direction in the planned research concerns studying mechanotransduction during ENS development and elasticity of the gut tissue (Axis 3). Although the future team leader has already published some work on the biophysical properties of migrating cells, for this aspect of the work several interactions/collaborations with local and international partners (IMRB, Singapore) to carry out biophysical approaches and analyses of biomechanical properties of the gut have been established. The PI joining from UPMC will become part of this subgroup and he will not be developing individual projects. Together they will focus on cadherin-integrin cross-talk and their impact on ECM composition and rigidity. This movement makes sense as there was some overlap in the previous organisational structure and it will only strengthen the overall grouping by combining them in this way. Going forward for the next 5 years, this axis will address biomechanical aspects of ENS development in normal and disesase situations. Studies on the mechanical properties of normal and pathogenic gut should provide novel and interesting data, and few, if any, groups elsewhere in the world are as well equipped to perform the proposed experiments bearing in mind their collaboration with biophysicists. It will be interesting to distinguish in normal and pathogenic gut if changes in the viscoelastic properties of the gut are a cause or a consequence of disease. For example, joint hypermobility is associated with gut functional disorders (e.g. Ehlers Danlos Syndrome type III (EDS III) with these defects resulting from a possible shared connective tissue disorder. As such, it would be extremely beneficial to be able to carry out biophysical experiments using gut tissues obtained from human patients with various gut motility defects. Further studies, that necessitate close collaboration with a team of biophysicists, who will in fact lead aspects of the work, will analyse the relationship between mechanotransduction and migration, particularly during ENS development. These studies will reveal whether deformations or constraints on the gut will affect the migration of enteric NCC through this tissue, and measure the forces that enteric NCC exert on the gut as they migrate through it. It will be interesting to see if such forces differ between “normal” enteric NCC and enteric NCC obtained from ENS mutant mice that may be less able to migrate and are compromised in some way. Other biomechanical studies will analyse how gut environmental stiffness effects the migration of ENS progenitors through/within the gut, and will identify new effectors of adhesion crosstalk during mechanosensing following stretch. These latter studies, which nicely combine cell/molecular biology with novel biomechanics studies, will shed light on the roles of various biophysical processes during normal and abnormal ENS development.

Conclusion

- **Strengths and opportunities:**

The complementary skills of PIs within the team and the large panel of expertise should facilitate fund raising. The unique ability to bring together molecular, cellular, developmental biology and biophysical experts to look at how the mechanical properties of the gut may impinge on ENS development and disease is a particular strength. The lack of competition in this area of research can be regarded as an opportunity and any paper generated could become highly cited. The strong grouping and interactions with established national and international collaborators should ensure success of the experiments and help to raise the group’s international profile. For the genetics aspect, there is good opportunity to capitalize on the existing large cohort of neurocristopathy patients.

- **Weaknesses and threats:**

- Biomechanical “force measurement” experiments are likely to be challenging to perform, and there is currently little data on the biomechanical properties of the gut and/or enteric NCC, particularly at a tissue or in vivo level.

- There is an insufficient technical staff to support the numerous projects.

- The committee recommands to develop common team projects versus individual PI projects.

- Difficulties, including logistics, arising from the establishment of a new grouping can be anticipated.

- **Recommendations:**

International visibility and attractiveness of the team have to be developed. More international exposure and grant income could help grow the group to a level where the ambitious objectives could be achieved. The team is encouraged to participate in European calls since there is already some international collaboration in place.

Team 17: Transfusion and red blood cell (RBC) disease

Name of team leader: Ms France NOIZAT-PIRENNE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	4	5
N2: Permanent EPST or EPIC researchers and similar positions		3
N3: Other permanent staff (without research duties)	4	10
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1
N6: Other contractual staff (without research duties)	4	4
TOTAL N1 to N6	**13**	**23**

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

• Detailed assessments

Assessment of scientific quality and outputs

This is a new team composed of 3 former entities that focus on sickle cell disease (SCD) and thalassemia. The scientific quality and output of the contributors to this new team is excellent. This emerging team combines 3 former units involved in studying different aspects of red blood cell (RBC) disease and pathophysiology and has a special focus on sickle cell disease (SCD). Of special note is the establishment of what is likely to be the world's largest cohort of patients with SCD with carefully obtained clinical phenotype information, laboratory data and a repository of biologic samples. This unique resource, under the leadership of a professor at the Henri Mondor Hospital has been the basis for many of the studies reported in the previous 5 years. It will also serve as a vital resource in many of the studies planned for the next 5 years. Members of the team have published 94 original articles and 9 reviews in the prior 5 year interval including papers in J Biol Chem, Blood, Transfusion, Am J Haematol, Plos One, Haematologica, out of which 30 are signed as first or last author. As an example of quality and excellence, the high profile paper on pulmonary hypertension in SCD (N Engl J Med, 2011) could not have been done without the Creteil SCD cohort established during many years of careful data collection. The same can be said for the paper that related erythrocyte density and certain clinical features of SCD (Blood; 2012). Work on the complications of transfusion in SCD, a major form of treatment and one with many difficult complications, is only possible because of the many patients treated at the Henri Mondor Hospital and the leadership of the team leader who has the infrastructure at the blood bank laboratories, the insights into this problem and the foresight to study this carefully. Her work lead to an invited review (Blood, 2012), setting out for the field the best means of management.

Assessment of the unit's academic reputation and appeal

There is a high level of international respect for the transfusion-related work and the many papers that have been published based on the study of the SCD cohort. Team members, especially the senior leaders are invited to important national and international meetings to discuss their work as both have made unique contributions to the field of SCD. The team leader is a world leader in the antibody-mediated hemolysis in transfused patients with SCD.

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

Members of the team are sought after by industry and pharmaceutical companies seeking collaborations to test device development and therapeutic trials. It is well known in the community for the breath of services it provides. The SCD unit interacts with community organizations, for example to promote blood donations among minorities. This is vitally important as difficulties with blood transfusion are a major problem in SCD. The team leader has also a national responsibility to optimize transfusion safety in SCD.

Assessment of the unit's organisation and life

As this is an emerging entity composed of 3 former entities, it is premature to forecast how it will evolve. The organization as it is presently constitued is excellent. Good leadership is in place and the contribution of the individuals involved has been excellent so one can be optimistic that it will come to have a sterling record. The team will be brought together in new laboratories at Henri Henri Mondor.

Assessment of the unit's involvement in training through research

The researchers of the team are very active in several master degrees. 4 PhDs have been defended over the last 5 years period whereas 2 are still ongoing. The team's involvement in training appears excellent, in a field that is worldwide recognized as poorly attractive for young scientists.

Assessment of the strategy and the five-year plan

The 5 year plan is very good and 2 themes are particularly attractive. The team will work in a new laboratory at the University of Paris Est Creteil in the EFS Cellular Therapy Centre located in the Henri Mondor Hospital. Some of the questions being asked about antibody-mediated hemolysis in transfused patients with SCD are very important and their solution would be a big advance in reducing SCD morbidity. Theme 5 has the potential to provide new and

interesting information about the genetic elements that affect the phenotype of SCD, besides those modulating HbF gene expression. The successful conclusion of this work will require careful coordination among clinicians, bioinformaticians and the core facilities that will provide high-throughput genotyping services. A lack of detail of exactly how this will be accomplished, how the work will be replicated and what functional studies will be done, reduces the attractiveness of this theme. Dense RBCs (DRBC) are apt to be important in SCD. It is not totally clear if they are the cause of pathophysiologic abnormalities or the result. The group has published in this area (Blood 2012). In the work proposed, the involvement of DRBCs in hemolysis and vascular damage will be studied, focusing on O_2 transport in DRBCs, hemolysis and oxidative stress, and complement activation, endothelial damage and the effects of transfusion on DRBCs. Guidelines governing when and how much to transfuse patients with SCD are few. The most interesting part of this theme is the aim to study *in vitro* the effect of transfusion on viscosity and adhesion to endothelial cells using mixtures of control RBC from healthy donors and RBCs from SCD patients with different numbers of DRBCs. This might permit the better understanding of the effect of transfusion and perhaps eventually allow the amount of blood transfused to be calibrated with the percent DRBC in the patient avoiding the precipitation of adverse effects related to hyperviscosity. This is an outstanding project by a leader in the field. Hemolytic transfusion reactions are a big problem in SCD, especially the delayed reaction where both transfused and patient cells are destroyed; a causal antibody is not recognized in a third of cases. A better knowledge of alloimmunization mechanism should permit other type of prevention. The PI hypothesizes that the damaged cells could be destroyed through the activation of the alternative pathway of complement that does not require antibody binding. The project to (i) identify the mechanisms of alloimmunization, (ii) determine the efficiency of anti-CD20 to inhibit alloimmunization in patients, (iii) study the epidemiology of delayed hemolytic transfusion reaction (DHTR) and explore its different mechanisms, (iv) characterize the variant blood groups and develop molecular tools to genotype patients' blood groups is outstanding. Both animal and human studies will be done. Based on data that showed correlation between some antigen specific RBCs alloimmunization and MHC class ll molecules expressed by the patient, they plan to look for correlation of the main immunogenic antigens involved in alloimmunization in SCD to permit a characterization of a risk factor for a specific MHC class II molecule expressed by the patient that can bind the dominant peptide and therefore implement specific prevention if the patient is a high responder. Aspects of therapy will also be examined like following patients who already received anti CD-20 to prevent recurrence of alloimmunization. An ongoing study of DHTR will be used to focus on new risk factors and hypothesis of immunization and DHTR. Complementing other themes, this work can study the role of DRBCs, polymorphism of the SIRPα receptor of CD47 on macrophages, the activation of the alternative complement pathway and polymorphisms in its fractions that protect against activation.

Conclusion

- **Strengths and opportunities:**

- This group has been highly interactive with basic science, clinical and translational science components.

- The new team structure will provide enhanced opportunities to interface and perform research across this wide spectrum and improving care in SCD. Opportunities for medical breakthrough and commercialization exist.

- This team receives outstanding support from the PI presence at the Henri Mondor Hospital where he has established the largest and most comprehensive hemoglobinopathies unit in Europe, if not the world. This provides a rich resource in patients and their clinical and laboratory data for all of the goals of this team.

- Some of the questions being asked about antibody-mediated hemolysis in transfused patients with SCD are particularly important and their solution would be a big advance in reducing SCD morbidity.

- The team leader is a world leader in this area.

- Theme 5 has the potential to provide new and interesting informations about the genetic elements that affect the phenotype of SCD, besides those modulating HbF gene expression.

- **Weaknesses and threats:**

- The continued support of the director of the "Unit of Genetic Diseases of the Red Cell" (UMGGR) at Henri Mondor Hospital is critically important and perhaps subject to the vagaries of external funding.

- The genetic studies could be inconclusive given the numbers of cases that will be studied.

- Little description of the genetic studies is provided.

- Some of the studies of RBC density and α hemoglobin stabilizing are not especially innovative.

- Neuroglobin and cytoglobin studies have a lower priority and do not fit particularly well with the SCD studies.

- Some people and laboratories involved have yet to move to Creteil and the status of the laboratory is unclear. Given the delays and changes often associated with this type of move, having one team located away from the main body of investigators could be problematic.

Team 18: Drug Discovery and Cell Therapy in Cardiovascular Disease

Name of team leader: Mr Roberto MOTTERLINI

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	1	2
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	5	5
N6: Other contractual staff (without research duties)	1	2
TOTAL N1 to N6	**7**	**9**

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

• Detailed assessments

Assessment of scientific quality and outputs

The team is a newly established research group in the unit (since 2012). The group was created after recruitment of the team leader by INSERM in January 2012 as a DR2. The new team will combine the expertise of the team leader on the therapeutic applications of the heme oxygenase-1/CO pathway and of one CR1 INSERM on cell stem therapy. The team leader is internationally recognized in the field of heme oxygenase and its role in heart function and cardiac diseases. In particular, he has pioneered the identification and development of water-soluble CO-releasing molecules (CO-RMs) for therapeutic applications. His team has also identified chemical features of compounds that may serve as inducers of heme oxygenase-1 (HO-1). This work is thus highly relevant for drug development dedicated to protecting vascular endothelial cells against the damage due to oxidative stress and injury. Over the last 5 years, an impressive number of papers has been published by the team leader as first or last author (50). He has also contributed to many as co-authors. These are mainly articles in specialized journals (i.e., Antiox Redox Signal, Atherioscl Thromb Vasc Biol, Pharmacol Res, Biochim Biophysis Acta, Crit Care Med, Pharmacol Research) but there is also an invited review in a high IF (Nature Drug Discovery) in 2010. Two recent Stem Cells papers signed by the other PI as last author have been published.

Assessment of the unit's academic reputation and appeal

The team leader has an excellent academic reputation. Since 2008 he has been invited to 22 meetings as speaker including a FEBS lecture award in 2011, and the second PI was invited to give a lecture at the Annual Meeting of the European Society of Cardiology in 2013.

The team leader also acted as member of the organizing committee of the 6th International Conference on Heme oxygenase (Miami) and one PI co-organized the 7th International Conference on Heme oxygenase (Edimbourg). Team members are reviewers for national and international grants.

Several team members are members of the European COST Action on gaseous molecules (European Network on gasotransmitters « ENOG »).

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

The team leader is involved in founding of the private company hemoCORM. Have to be mentioned one patent filled and one in progress on the CO-Releasing Molecules technology and 2 patents filled on Stem Cells Technology.

Assessment of the unit's organisation and life

The New team will include 1 INSERM director of Research, 1 INSERM Established Investigator (CR1),1 Senior Scientist, 5 Post-doctoral fellows and 1 PhD Student.

Assessment of the unit's involvement in training through research

Since 2008, the PI trained 10 Master (M1/M2) students, 4 PhD students and 1 engineer student.

Assessment of the five-year plan and strategy

The project combines structural approaches to design novel CO-releasing molecules (RM) and in vitro and in vivo experiments to investigate the role of Heme Oxygenase-1 and CO in oxidative injury, inflammation and stem cells regenerative properties in the heart. The project is organized in 4 main objectives. The first two objectives are the logical follow up of already performed work concerning CO-RMs and HO-1 inducers. An interesting opening seems to come with CORM-401 compound releasing 3 molecules of CO. This and few other compounds will be studied in macrophages, cardiomyocytes and endothelial cells for cytotoxicity and effects on inflammation. Also creating hybrid molecules that deliver exogenous CO and simultaneously enhance the endogenous production of CO via HO-1 induction is highly innovative (patent pending).
Importantly, plans are also designed to take advantage of the CR1 expertise. In particular the objectives 3 and 4 are dedicated to determine the role of the HO-1/CO axis in the regenerative properties of mesenchymal stem cells and to

implement therapeutic approaches combining the use of new compounds with stem cell technologies to treat cardiac dysfunction and inflammation. Although the role of HO-1 in mesenchymal stem cells has been reported by other groups, the benefit of such a combined strategy needs to be demonstrated.

Conclusion

- **Strengths and opportunities:**

- The team leader has a leader position in CO-RM compound design and applications.

- The scientific productivity of the team is effective.

- The team has strong skills in chemistry of CO-releasing molecules.

- **Weaknesses and threats:**

- The team has insufficient competences in cell biology of cardiac and inflammatory cells.

- There is an insufficient use of relevant animal models.

- **Recommendations:**

- There is a need to extend collaborations with private partners for improving the development of novel CO-releasing molecules.

- The team has to recruit scientists with strong competences in cell biology of cardiac and inflammatory cells.

- Establishing collaborations with groups expert in cardiac diseases and inflammation needs to be integrated in the policy of the team.

5 • Conduct of the visit

Visit dates:

Start: 20 january, 2014, 9:00

End: 23 janauary 2014, 17:00

Visit site: Faculté de Médecine de Créteil

Address: 8 rue du général Sarrail, 94000 Créteil

Conduct or programme of visit:

Day one - 20 January 2014	
9:00	Welcome (closed-door) Visiting committee with the AERES Scientific advisor
9:15	**AERES representative**: the role and procedures of AERES
9:30	**Direction of the Center:** Past and future; Discussion
10:30 - 10:55	Coffee break
	Department for NEuroSciences and PsychiatRY (ESPRY)
10:55	**Short presentation of ESPRY Department (Mr Fred RELAIX)**
11:00	Team Talk and discussion with the team leader
	Name of the team leader: Ms Marion LEBOYER
11:55	Team Talk and discussion with the team leader
	Name of the team leader: Mr Stéphane PALFI
12:50-13:05	closed meeting
13:05	Lunch
13:45	Team Talk and discussion with the team leader
	Name of the team leader: Ms Anne-Catherine BACHOUD-LEVI
14:40	Team Talk and discussion with the team leader
	Name of the team leader: Mr Jean-Pascal LEFAUCHEUR
15:35	Team Talk and discussion with the team leader
	Name of the team leader: Mr Frederic RELAIX
16:30-16:45	closed meeting
16:45	Coffee break
17:00	**Parallel meetings with personnel:**
	Discussions with engineers, technicians, administrative
	Discussions with staff scientists
	Discussions with students and post-docs

Day two: 21 january 2014

Department « Pathophysiology of cardiovascularand respiratory diseases, development and senescence » (PhyDeS)

8:30	**Short presentation of PHYDES Department (Mr Serge ADNOT & Ms Sylvie DUFOUR)**
8:35	Team Talk and discussion with the team leader
	Name of the team leader: Mr Bijan GHALEH
9:30	Team Talk and discussion with the team leader
	Name of the team leader: Mr Jorge BOCZKOWSKI and Ms Sophie LANONE
10:25-10:35	closed meeting
10:35	coffee break
10:50	Team Talk and discussion with the team leader
	Name of the team leader: Mr Serge ADNOT
11:45	Team Talk and discussion with the team leader
	Name of the team leader: Ms Pascale FANEN
12:40-12:50	closed meeting
12:50	lunch
13:45	Team Talk and discussion with the team leader
	Name of the team leader: Ms Sylvie DUFOUR
14:40	Team Talk and discussion with the team leader
	Name of the team leader: Mr Bruno LOUIS and Mr Marcel FILOCHE
15:35-15:45	closed meeting
15:45	coffee break
16:00	Team Talk and discussion with the team leader and closed meeting
	Name of the team leader: Ms Françoise NOIZAT-PIRENNE
16:55	Team Talk and discussion with the team leader and closed meeting
	Name of the team leader: Mr Roberto MOTTERLINI
17:50-18:00	closed meeting

Day three: 22 january 2014

Department VIC

8:30	**Short presentation of VIC Department (Mr Philippe GAULARD)**
8:35	Team Talk and discussion with the team leader
	Name of the team leader: Mr Yves LEVY
9:30	Team Talk and discussion with the team leader
	Name of the team leader: Mr Jean-Michel PAWLOTSKY
10:25-10:35	closed meeting
10:35	Coffee break
10:50	Team Talk and discussion with the team leader
	Name of the team leader: Mr Philippe GAULARD

11:45	Team Talk and discussion with the team leader
	Name of the team leader: Mr Alexandre DE LA TAILLE
12:40	Team Talk and discussion with the team leader
	Name of the team leader: Mr Djillali SAHALI
13:35-13:50	closed meeting
13:50	Lunch
15:00	Discussion with the representatives of the managing bodies
15:45	Discussion with the head of the center

Day four: 23 january 2014	
9:00-17:00	**Private meeting of the visiting committee (in presence of the AERES scientific advisor)**
17:00	End of the visit

6 • Supervising bodies' general comments

UNIVERSITÉ PARIS-EST CRÉTEIL VAL DE MARNE

UPEC Connaissance - Action

Réponses au Comité d'Experts AERES suite à l'évaluation
UMR-S 955 Institut Mondor de Recherche Biomédicale (IMRB)

Tite de l'unité : **Institut Mondor de Recherche Biomédicale**
Label demandé : **UMR-S**
Nom du Directeur : **Dr Jorge Boczkowski**

EVALUATION OF THE CENTRE

The direction of the Centre would like to thank the Committee for the very detailed and constructive analysis of IMRB's past activities and project. The Centre very much appreciated the positive global assessment of the unit and its five-year plan and strategy.

Indeed, the Committee highlighted "*the excellent international reputation of IMRB teams, the excellence of their scientific production, the Centre's impressive capability of accessing important funds from various local, regional, national and international sources, the Centre's deep involvement in research training, the access of teams to technological platforms, and patient cohorts, and the resulting attractiveness of scientists and students".* Moreover, the Committee considered that the five-year scientific plan and strategy is logical and adequate and that the consequent evolution of the Centre management is appropriate.

The Committee made several comments that we grouped by subject and, each time, made a unified response. Collectively, the direction of the Centre fully agrees with the spirit of the comments.

Internationalization of the Centre

The Committee noticed that although most of the teams have confirmed international visibility, the Centre itself has an intermediate level of internationalization. This comment is well received, and the direction of the Centre already began to actively work on this issue. The following measures are to improve the internationalization of the Centre:

1. Fostering our participation in European projects through hiring a specialized consultancy with the support of the School of Medicine ("PNO consultants", as announced in document S2-1-1-UR, page 12). Since we began to work with PNO (January 2014) one letter of intention for a H2020 integrated project has been proposed by Prof Derumeaux as coordinator (Serge Adnot team) involving also R Motterlini's team, and another is under preparation by Prof J Cohen (Dil Sahali team). In addition, IMRB teams participate as partners in two other H2020 projects.

2. Improving participation in Marie Curie fellowships, with the support of PNO consultants also.

3. Setting up regular conferences by renowned international scientists in order to increase the visibility of the Centre (see later).

Measures 2 and 3 will be implemented in the upcoming period.

In addition to these steps taken by the Centre, the University:

- *At the European level, is setting up measures to improve the internationalization of its laboratories, by for example, organizing a series of meetings of research team*

directors with the National Contact Points of the different instruments of the H2020 programs. The goal is to develop the participation of the teams in European projects and to supporting invitations of foreign scientists by the teams.

- *At the international level, setting up collaborations with East Cost US Universities: Brown and Columbia Universities and Japanese universities facilitated by the recent convention signed between the French and Japanese governments.*

The Committee recommended an English web site of the Centre. This is already the case, the website of the IMRB exists in French and English since the very beginning of the IMRB (http://www.imrb-en.u-pec.fr/). To increase its visibility and allow a better internationalization of the Centre the website will be improved.

Relation with industrial partners

The Committee recommended to further stimulate contracts with industries for all groups. The Centre agrees with this comment, but as pinpointed by the Committee in the paragraph "Global assessment of the unit" (AERES report, page 6), the teams of IMRB have already many contracts with industries. Moreover, although not all the scientific programs can benefit from strong interactions with industries, the direction of the Centre has already begun to take initiatives to further develop contracts with industry. The first actions were: 1) to develop the relation of the teams with the "Société d'accelération et transfert de technologie" Ile de France Innov (SATT idfinnov, a public society devoted to transfer of knowledge from academic labs to industry). It has to be noted that periodic meetings between the teams and the SATT were scheduled; the first was on March, 6th and since then 4 projects have been examined for filing a patent, and 2) to strengthen the relation with the "Conseil Général, " du Val de Marne, and the "Chambre du Commerce et de l'industrie" which can make a link between the teams and industries located in the Val de Marne department. The Committee's recommendation of organizing seminars with industries is already in progress (Tecsanté network).

The University has decided to promote its lab's scientific platforms among industrial partners. By allowing industrial access to scientific platforms, the goal is to trigger new partnerships. The Direction of research and the Direction of communication have both been working on that project, under the supervision of the research vice-president and the business vice-president.

Finally we have to mention that some teams are in permanent contact with Inserm Transfert. In this context, 24 international patents and 8 computer software have been filed in the last 5 years.

Full time scientists

The Committee remarked that regarding the size of the Centre, there are few permanent full time scientists. This is a point we strongly agree with. The direction of the Centre is conscious of this situation and an active policy to attract and recruit full time scientists has been developed in the last 2 years. As a consequence, as detailed in document S2-1-1-UR (page 10), 11 new full time investigators have joined the Centre for the new project. The efforts to recruit and attract new full time scientists will be pursued and enhanced during the next five years. Moreover, it must be underlined that IMRB is located in a strong clinical environment, and consequently many clinicians develop their projects in the different teams. This gives IMRB a very specific translational research orientation.

Management of Centre

The Committee stated that the management of the Centre is weak, or, for some aspects, non-existent in several domains such as, distribution of the budget and of the technical manpower across the teams or scheduling for scientific applications to ERC, INSERM. The direction of the Centre disagrees with most of the points of this comment. For example, the criteria governing distribution of Inserm and UPEC funding by the Centre direction among the teams was clearly explained in document S2-1-1-UR (page 3, paragraph "Funding and staff

evolution") and during the presentation of the Centre. Concerning distribution of technical manpower across the teams, priority is given by the direction of the Centre to the common facilities and transversal functions,.

In spite of this discordance with the Committee, the Centre direction is clearly conscious that the management of the structure must be adapted to the new scientific organization to further increase the added value of the Centre. Consequently, the Centre is now building governance based on the action of a direction committee composed of the Centre director, the general secretary, and the Heads of the departments and DHU (see document S2-1-1-UR, page 12). The committee began to work before the AERES visit; it meets twice a month, and addresses most of the issues raised by the AERES committee. Among other actions, the Centre committee is also now working on i) internal rules for application to grants and positions (including ERC grants with the support of UPEC), ii) on the development of scientific animation (it has already identified a senior full time scientist researcher that will be in charge of this action, organizing regular national and international Centre seminars and transversal summer/winter school for PhD students and post-docs), and iii) on fostering communication and visibility (as for example improving the Centre web site engaging a specialized consultant).

Interaction between teams and with the CIC and clinical departments

The Committee recommended to stimulate the integrated research among the teams and departments. We agree with this point that we already identified as a shortfall. As mentioned, different measures will be set up to promote synergies between the teams and the departments (already indicated in document S2-1-1-UR, page 11): the Centre will launch an internal call for proposals to bring out collaborative projects, and shared PhD between two teams will be supported. The scheduled summer or winter transversal thematic school for PhD and postdocs will also be a possibility to stimulate interactions between teams.

A priority of the Centre and of the Faculty of Medicine is to stimulate the interaction of the IMRB with the CIC and the clinical departments. These issues will be further developed during the next 5-year period through, at least in part, the development of the research activities of the DHUs. Moreover, the Faculty of Medicine is setting up a new organization of the translational research, which will include all the actors involved in.

PhD students and Postdocs

The Committee stated that the administrative integration of PhDs and PostDoctoral fellows as well as advanced courses dedicated to them are either insufficiently promoted or inexistent, respectively. We fully disagree with this comment. In addition to training organized by the research teams, the administrative and financial support of a PhD and Post-Docs association (namely CoDoPoDo), different actions have already been taken by the direction of the Centre to ensure the administrative integration of PhDs and Post-docs (document S2-1-1-UR, page 10): at least three meetings for new incomers are held each year, a welcome booklet in French and English is given to each new incomer, and the Center also ensure the formation of these agents in the field of security. The advanced courses for PhD students and Post-Docs are essentially under the responsibility of the doctoral school; however the scheduled summer or winter transversal thematic school the Centre is planning to organize will also contribute to the formation of the PhD and Post-Docs.

Platforms

The Committee stated that several platforms (bio-informatics, bio-statistics, screening...) are still missing. As described in document S2-1-1-UR page 13, the direction of the Centre is in the process of setting up a NGS platform and a bio-informatics-bio-statistics facility with the support of UPEC and Inserm. Both facilities should be functional in the upcoming fall. In addition, as indicated during the visit of the Committee, the Centre is discussing with the direction of the CRRET laboratory located in the faculty of science of UPEC, to have a favored access to a peptidomics platform recently installed in this structure.

We deeply disagree with the Committee recommendation on the need to set up guidelines for using platforms. Indeed, those guidelines are already provided, as IMRB has developed a pioneering action, as an Inserm unit, for the development of the quality approach for the platforms. Three out of five are now granted Iso 9001, which by definition provides users with precise guidelines and ensues a continuous follow up and analysis of their activity. Extension of the qualification to the other platforms is scheduled for the upcoming years.

Administrative support and premises

The Committee noticed that Centre staff complains about the lack of an efficient administrative and secretarial support and recommended to strengthen the administrative resources of many teams. Staff complains are essentially due to the diminution of several permanent positions (minus 9 out of 33 administrative or platform positions since 2007) and the difficulty for IMRB to replace these positions by non-permanent staff, often poorly qualified, on its own funds (i.e. nearly 100 000 euros in 2013). This diminution of the permanent positions (which also concerns the technical support of the teams) is independent of the policy of Centre. It has to be noted, however, that in spite of this major limitation, the direction of the Centre is actively working on improving the efficiency of the administrative and secretarial support of the teams for the next period by promoting different measures such as, extending the quality approach to the whole administrative process of the Centre.

The Committee recommended to quickly gather all the teams at the same place, with the exception of the Veterinary School, and to distribute the spaces according to the real needs of the teams. As stated in document S2-1-1-UR (page 13), this is a main objective of the direction of the Centre. Management of real state assets of the Centre is under the control of UPEC, which is in charge of elaborating and executing plans in order to accomplish this objective. Premises refurbishment for hosting S Dufour and F Relaix teams and M Marden group is scheduled for the end of 2014.

The direction of the Centre hopes that the supervising institutional bodies will support it in improving administrative support and teams location, which are both critical issues to ensure the development of a modern and dynamic research Center of excellence.

In conclusion, the direction of the Centre would like to thank again the Committee for their positive and constructive comments and hopes that the answers will reassure the Committee about our capacity to develop successfully the project for the next 5 years.

EVALUATION OF THE TEAMS

Team 1: Translational research in genitourinary oncogenesis

Team leader: Mr Alexandre de la Taille

The Team 7 would like to thank the experts for their time and for their evaluation. We agree on the report but we would like to address some comments:

'Recommandations'

Point 1: Our Prostate Cancer presentations exposed our achievements but also the ongoing projects and we agree that many projects were presented. However the future objectives will focus only on 4 projects: dermaseptin, hormonal environment, neuropiline and signature of aggressive prostate cancer.

Point 2: Concerning a possible collaboration with immunologists from our institution, we would like to say that we already plan to work with the immunologists for the project on inflammation and bladder cancer

Point 3: the Experts suggested to increase the number of seniors but we would like to mention that 4 new researchers just arrived on January 2014 including a full time researcher (Dr M Amiche) with his expertise on peptidomic.

Point 4: concerning the collaboration with strong other groups, we would like to mention that our projects include strong collaborations with Curie Institute (Dr Radvanyi and Dr Aturo), La Ligue Contre le Cancer Carte Genomique and the GDR on peptidomic

Team 2: Immunology and oncogenesis of lymphoid tumours

Team leader: Mr Philippe Gaulard

We are grateful to the experts of the Committee for their comprehensive review of the project of our team and their positive comments on our scientific project and our achievements.

We have addressed the recommandation made by the committee: " The team has to increase collaboration with experimental transplantation team (mouse/human) working on immunomodulation of alloimmunity".

This issue relates to the theme developed on the immunoregulatory role of IL4I1 in the context of tumour surveillance, particularly in follicular lymphoma. We agree with the committee that it will be interesting to investigate the immunomodulary functions of IL4I1 in the context of transplantation. For that purpose, we have initiated discussion with Dr Jose Cohen, leading the Transplantation group (Djillali Sahali team). This group has developped suitable *in vitro* and *in vivo* experimental models that will allow to test whether or not our immunomodulation strategy relying on IL4I1 effect could also be applied in the field of transplantation. This will be the basis of a future collaboration between our 2 teams with complementary expertises belonging to the VIC Department.

Team 3: From pathophysiology towards immune---based interventions in HIV infection

Team leader: Mr Yves Levy

The team would like to thank the Committee for the precise and fruitful review of the scientific program and activities. We have addressed all the comments made by the Committee and have listed our answers and views below:

1) The Committee raised the point of the vastness of the program as a potential threat as well as the capacity to develop 4 or 5 vaccine strategies. We believe that the originality of our scientific program is the continuum from basic science to clinical trials illustrated by the number of ongoing clinical trials developed by the team. This originality is also attested by the high number of patents (more then 10) defended by the team in the last five years. We would like to mention that since the presentation to the AERES Committee in February 2014, two vaccine clinical trials have started, the LIGHT and VRI01 trials, involving approximately 200 people (HIV infected and healthy volunteers), testing three candidate vaccines (DNA-HIV, ANRS MVA and ANRS HIV-Lipopeptide). Another trial using *ex vivo* dendritic cells associated with IL-7, the DALIA II trial, already in discussion with the regulatory agency, is in preparation and will be launched in the second half of year 2014. We are confident that this will reassure the Committee about the capacity the team has to develop the portfolio of the vaccine candidates presented in February. Moreover, as today the scientific trend is to promote prime-boost immunizations in prophylactic and therapeutic vaccinations, global strategies implie the need of developing a series of vaccines.

2) Regarding the minor potential problems mentioned by the Committee, we would like to clarify that we share the concerns of the Committee about the capacity for Europe to use NHP but also other animal models for pre-clinical studies. Unfortunately, HIV infection in animal models is restricted to NHP and humanized mice models. Furthermore, regulatory agencies may ask for informations concerning NHP immunogenicity and challenge studies to proceed to human clinical studies. At the moment the strategy of Team 3 and the VRI is to perform pre-clinical trials in collaboration with the NHP animal facility ABL in Rockville, Maryland, USA. Moreover, we would like to mention that thanks to the new position of Prof J. Banchereau at UPEC within the team and at Jackson Laboratory in USA, we have already planned to develop adequate humanized mice models.

3) Finally, the Committee raised the point on “the philosophical potential critique… “ that the Team may diversify its scientific program and starts new lines on pathologies other than HIV”. We believe that this statement contradicts somehow the concerns about the vastness of the scientific program we are developing and the final recommendation to focus on objectives and strategies. Given the current global challenges for the development of a vaccine against HIV and the understanding of the pathology, which persists despite the advent of potent ARVs, we need to focus and gather all efforts on these scientific objectives because it is the only guaranty to succeed and fight HIV.

Team 4: Pathophysiology and therapy of chronic Viral Hepatitis and related cancers

Team leader: Mr Jean-Michel Pawlotsky

We are extremely grateful to the AERES panel for their very positive assessment of our scientific and organisational achievements and of our 5-years strategic research plan. We also appreciate their comments and fully share their vision.

Our top priority in the short-term is to fully integrate the new members. Everybody has now joined the same lab space. The complementarity of expertise, that fulfils well-known needs of the team, and the in-depth investment of all old and new members in the collective team's project is a guarantee of success of the research team, which already functions as if the new members had always been there. Our goal is indeed to sustain the innovative nature and the productivity of our research program while moving further into the competitive field of liver carcinogenesis and hepatocellular carcinoma management. In this respect, we appreciate the panel's trust in our vision and leadership to achieve these goals. We also fully agree that more permanent positions at the engineer/technician level are needed to support our strategic plan, and hope that both INSERM and the UPEC University will support us in this endeavour.

We completely agree with the recommendations of the panel. We do want to actively pursue the recruitment/stabilization of the existing senior scientists that already lead successful and strategic research projects, and hope that we will receive support from INSERM and the UPEC University. Reinforcing the research subgroup on liver cancer is a top priority, as we believe this is a major strategic move for our research group. Finally, we are actually willing to further enhance our research capabilities by expanding our activities to include more HBV research in both basic virology and liver carcinology. We are currently seeking for experienced scientists in this field who could join the group and be recruited in the future, because this move requires very specific (and unfortunately rare) expertise. Once again, we do hope that both INSERM and the UPEC University will help us achieve this very important goal.

Team 5: Renal immunopathology and transplantation

Team leader: Mr Djillali Sahali

We would like to thank the Committee for their helpful comments and criticisms. The Committee considered that "*the team represents a unique context on the same site with strong and recently expanded scientific and experimental expertises, that team members have a strong implication in training with PhD students, and post-doctoral fellows and that team projects are very interesting and pertinent"*.

The Committee made some remarks and our responses are detailed herein:

We fully agree with the Committee's comments concerning the insufficient scientific interactions between our two main axes. Our team is still relatively young, mainly regarding the "transplantation" project. Consolidating the latter constituted the team's first goal, which has been achieved in terms of scientific development, as recognized by the committee.

We aim for the next 5 years to develop a central axis based on the respective competences of researchers from both groups. Our first project concerns the analysis of effector and regulatory B cell response in idiopathic and post-transplantation recurrence of nephrotic syndrome. Particularly, we have developed in our laboratory a functional and phenotypic analysis of regulatory B cells. The second project will combine the c-mip transgenic models developed in our laboratory with our expertise on T cell alloimmune analysis in order to better understand the mechanism of post-transplant recurrence.

This central project will be carried by PhD students and directed by Prs. P. Grimbert and V. Audard and is supported by our University.

About the difficulty, in general, to fund transplant research, our close links with industry have helped us so far not be hindered by this parameter. As mentioned by the committee, it is clear that we must have more success, particularly in European funding.

Finally, regarding the insufficient collaborations within international networks, we would like to respectfully mention that (i) we are strongly implied in the European NEPHRUTIX network (Efficacy of Rituximab For the Treatment of Calcineurin Inhibitors Dependent Nephrotic Syndrome During Childhood), (ii) have close collaborations on Tregs with two leader teams in Germany and (iii) We have recently established a long-term collaboration with Jiangsu University (China) for the exchange of students and personnel.

Once again, the team would like to thanks the Committee for its very interesting and helpful comments. We hope that the members of the committee will be convinced by our answers about our capacity to develop successfully the project for the next 5 years.

Team 6: Interventional neuropsychology

Team leader: Ms Anne-Catherine Bachoud Levi

We fully agree with the recommendations of the AERES. We are aware that the team needs to increase its staff by recruiting new researchers and technical staff. Along this line, we have recruited our first full-time researcher in 2011 (C. Jacquemot). M. Giavazzi, one of our post-doc will be candidate for a CNRS position (CR2) next year. We recently obtained a tenure of assistant Professor for Laurent Cleret de Langavant that will start in Sept. 2014. We also get support for clinics from staff that is not part of the research team (social worker, 2 psychologists, 1 doctor, & 1 secretary). In the next term, we will pursue our policy of recruitment and we expect to recruit new scientists and technical staff.

Team 7: Biology of the neuromuscular system

Team leader: Mr Fred Relaix

We fully agree with the work and recommendations of the AERES. Of note, 2 groups are part of the REVIVE labex (F. Relaix and S. Blot), and members of the team hold 13 HDRs and not 18 as indicated. Regarding the expertise of the last two groups, they have been complementary rather than redundant for more than a decade, and the new team will be of benefit for both of them. S. Blot group will continue to perform clinical research and preclinical trials in dogs, while L.Tiret group will continue to perform comparative medical and functional genetics in mouse, cat and dog models.
Other comments:

At the moment, a part of team members are dispersed into different geographical locations, which may negatively influence planned interactions.
We are currently working with UPEC in order to renovate 600m2 on the 5th floor of the UPEC medical school. In addition to project-based interactions, monthly scientific meetings have started last March and will become weekly meetings in January 2015. Besides, the Direction Committee of the team has already set up regular meetings to optimize the future renovated laboratory, accelerate global communications between the five groups and reinforcing the scientific strategy. Indeed members from 4 of the 5 groups have recently answered to a grant proposal as co-applicants.

There are complex ethical issues concerning using large animal models.
We are tackling these important issues, working in parallel with 2 Research Ethics Committees: ComEth n°16 (ENVA-UEC-ANSES) is dedicated to experimental protocols and ComERC to clinical protocols. Two members of the team are members of ComEth. In addition, we plan to develop research collaborations with Humanities researchers (sociologists and philosophers) interested in studying human-animal interactions. Our oblective is to develop a transdisciplinary research program focused on our collective limitations and willingness to tolerate the use of large animals in preclinical research.

Number of targeted NMDs appears very large and a prioritization of one or two of them would help in developing specificity/research identity of the team.
We will focus on a limited number of NMDs corresponding to our main clinical, pathological and animal models long-term expertise and interests (Centronuclear myopathies, Duchenne Muscular Dystrophy, inflammatory myopathies and Myotonic Dystrophy)

Attracting postdoctoral fellows can be improved considering team as a whole.
We are developping a general funding strategy with AFM for the team in order to hire additional postdoctoral fellows. Moreover, general and group-specific fundings will be promoted in order to attract students and post-docs.

A high proportion of teacher-researchers have heavy teaching duties
We are aware of this issue and will attract full-time young researchers. We are also planning to discuss the possibility of reorganizing some of the teaching programs in order to optimize the research time of some of our teacher-researchers. Besides, having teacher-researchers in the team will be key to identify and attract highly-motivated and skillfull students.

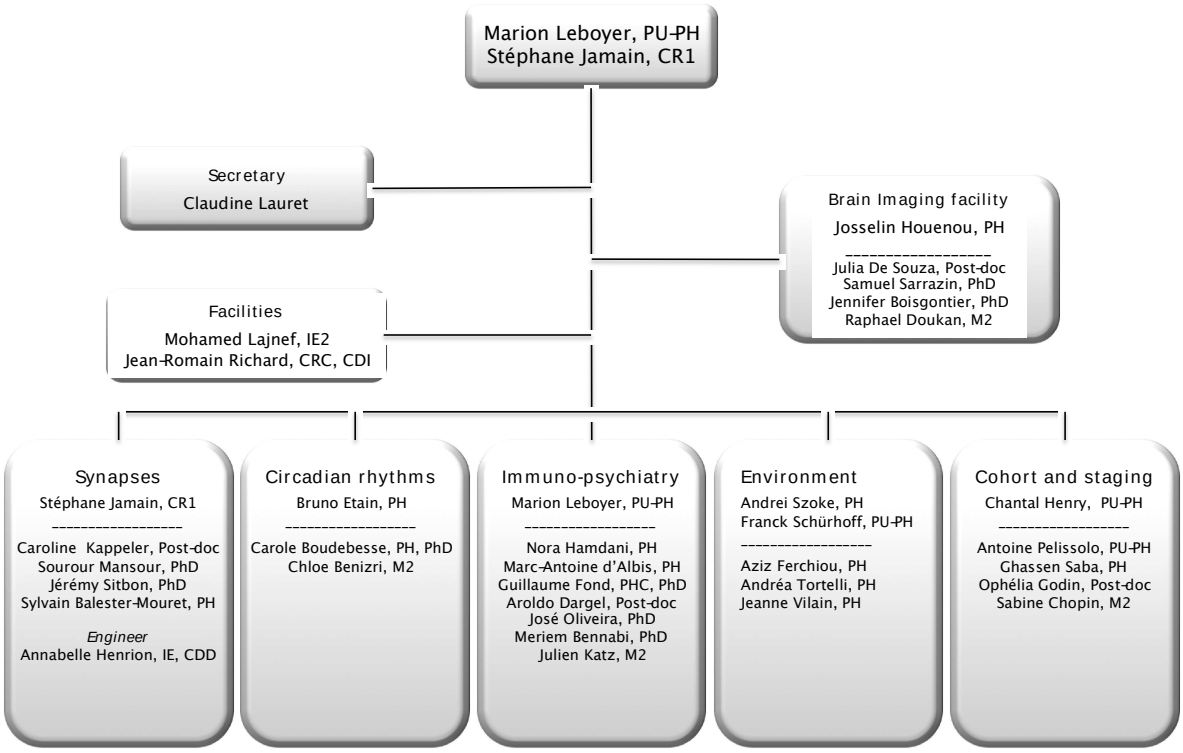
Team 8: Genetic psychiatry

Team leader: Ms Marion Leboyer

We thank the reviewers about their careful reading and the recommendation they made on our research plans. We would like to emphasize that our team will be headed by two complementary researchers, i.e. **Marion Leboyer** who will supervise clinical assessments and etiopathological explorations and **Stéphane Jamain** who will be in charge of the neurobiological and genetic investigations, in order to facilitate the translational approaches between the five research axes of the team. We will pay particular attention to develop as much as possible collaborations and overlaps between our five lines of research. For instance, genes involved in circadian rhythms and sleep/wake cycles (lines 1 and 2) will be studied in regards to their role on synapse formation and function (line 1) as well as relationships between sleep/wake cycles abnormalities (line2) and inflammatory responses (line 3). Moreover, genes implicated in immune modulation as well as biomarkers assessed in the Fundamental Cohort (Lines, 1, 3 and 5), will be studied in regards of environmental factors (line 4). Finally, brain imaging will be developed in each of the five lines of the team thanks to our transversal facility located at Neurospin.

We totally agree that the long-term objective will be to better understand the etiopathogeny of psychiatric disorders and this major aim of our team is illustrated in its new title itself, i.e. “Genetics and Pathophysiology of Psychiatric Disorders”. This will be ensured by the recruitment of a researcher, who will be in charge of developing cellular and animal models in regards to results that will be obtained in the five research lines. In addition, our team in collaboration with the other ESPRY teams, are currently generating a facility for electrophysiological studies, which will be located in the new animal house. Finally, the main aim of our Labex BioPsy is to develop collaborations between teams conducting clinical research and teams with expertise in basic neurobiology and three research projects have recently been funded illustrating these fruitful collaborations dedicated to deciphering the etiopathology of psychiatric disorders.

In order to provide more details on our organisational structure, you will find below the list of major team members with a brief description of their expertise.



Marion Leboyer: professor of psychiatry, team leader with expertise in clinical research in psychiatry.

Stéphane Jamain: geneticist, team leader with expertise in genetic and neurobiological exploration of psychiatric disorders.

Caroline Kappeler: post-doctoral position dedicated to neuron culture and animal behaviour.

Annabelle Henrion: engineer, expert in molecular and cell biology.

Bruno Etain: psychiatrist specialised in clinical exploration of bipolar disorder.

Carole Boudebesse: psychiatrist who has been trained in the Pittsburgh Psychiatry Institute on circadian rhythms and sleep abnormalities.

Nora Hamdani: psychiatrist who has been trained in the Laboratory of Immuno-Histocompatibility at Saint Louis Hospital (Paris, France) on immune-inflammatory assessment of patients.

Andrei Szoke: psychiatrist specialised in the environmental factors in psychotic disorders and in charge of the FP7 EU-GEI project.

Franck Schürhoff: professor of psychiatry specialised in research on schizophrenia.

Andrea Tortelli: psychiatrist who has been trained at the Institute of Psychiatry, King's College, London on epidemiology of environmental factors in schizophrenia

Chantal Henry: professor of psychiatry specialised on clinical exploration of patients with bipolar disorder.

Antoine Pelissolo: professor of psychiatry specialised in anxiety disorders and innovative treatment of resistant disorder

Ophelia Godin: post-doctoral position dedicated to epidemiological studies.

Josselin Houenou: psychiatrist specialised on brain imaging, in charge of the brain imaging research at Neurospin (CEA, Saclay, France) where he was trained.

Julia De Souza: post-doctoral position dedicated to brain imaging exploration of patients with psychiatric disorders.

Mohamed Lajnef: biostatistician.

Jean-Romain Richard: project manager.

Team 9: Restorative Neurosurgery using Biotherapies and Advanced Technologies in Neurology and Psychiatric disorders

Team leader: Mr Stéphane Palfi

We thank the reviewers about their careful reading and the recommendation they made on our research plans. Despite our strong interaction with other research group, we also feel that there is need to increase our permanent research staff. This aspect of the team development is one of our priority. Given the fact that we have signed numerous long term research contracts in 2013 (more than 10 years) and others 5 years duration, we are now in position to justify long term recruitment of research dedicated staff.
A post-doc, a clinical researcher, a research technician and an experienced MD, PhD. in neurological clinical research field with a strong expertise in neurogenetic will be recruited in 2014 (funding obtained for these positions). The MD, PhD should obtain a permanent position in 2016. In addition, discussions are underway with our support agencies to stabilize the position of our current researcher engineer in an INSERM position. On a longer term, we have the plan to recruit a PHU and PUPH research oriented within 5 years from now. We have identified the candidate who will be professor assistant in 2017. We will also apply for an MCU-PH position to reinforce our training program in research in functional neurosurgery and biotherapies.

Team 10: Peripheral and central nerve excitability and therapeutics

Team leader: Mr Jean-Pascal Lefaucheur

We thank the AERES committee for their careful reading and the recommendations they made on our research plans. We are grateful to the AERES committee for their positive assessement regarding the strengths of our team, i.e., the well-recognized expertise and international reputation of our team in cortical stimulation techniques, neuropathic pain and peripheral neuropathies, including small fiber neuropathies, associated with a very good publication track record of peer-reviewed publications and large involvement in training through research.

The committee raised that the basic research component is more limited than the clinical, technical or therapeutic aspects in our activities. Our research is obviously clinical and therapeutic research, but we are also clearly involved in pathophysiological research, in particular in characterizing activity-dependent axonal loss in inflammatory neuropathies, in defining small nerve fibre involvement in painful neuropathies, and in the understanding of mechanisms of action of treatment, regarding both immunobiotherapies (e.g., intravenous immunoglobulins) and neurostimulation (e.g., noninvasive cortical stimulation). Our group is focused on one specific "research-driven" question, which is the involvement of nerve excitability disorder in several neurological disorders, i.e. peripheral neuropathies, multiple sclerosis, and motor stroke, on their motor and sensory (including pain) aspects. To address this question, we have developed various neurophysiological methods. Our "research-driven" approach is quite visible, and for example, we are the leading research group that has explained the mechanism of action of motor cortex stimulation to relieve chronic neuropathic pain. This approach will be further developed and led us to plan specific recruitment to go deeper in the understanding of involved processes and mechanisms, on genetic, imaging, electrophysiological aspects. New and innovating projects will be conducted during our five-year plan (e.g., genetics of small fibre neuropathy or TMS investigation of motor cortex plasticity in neurovascular domain), with a basic research already organized in collaboration with very close groups (Jérôme Devaux, Marseilles, Nobouhiro Yuki, Singapore, or Anne Louise Oaklander, Boston, for example). Moreover, our objective is to propose translational research from experimental (murine) models in the next few years. We have already several opportunities to develop this type of research in close collaboration with external groups and, as underlined by the reviewers, our team will benefit from the restructuration of neurosciences research at IMRB and within the ESPRY department for this purpose.

Second, we have already addressed several points raised regarding the size and organization of our new team. Specifically, the head of the Department of Genetics in Henri Mondor hospital who will be recruited in September 2014, Pr Benoît Funalot, will be integrated in our research team. He is a well-recognized specialist of the genetics of the peripheral nerve, and our research on painful small fibre neuropathies will benefit from his expertise, especially on the underlying genetic origin of excitability disorders causing this type of neuropathy. This research has already begun with a M2 students involved in this field of research. In addition, the recruitment of a full-time researcher is our main objective in the next few years. Pending to this recruitment, we will reorganize our team in order to have a full-time researcher involved in the progress of our projects. Moreover a full-time research engineer will be recruited this year on a research budget allocated for at least three years. There is no doubt that this aggressive recruitment strategy (in genetics, imaging, electrophysiology) will lead to a rapid development of our research.

Third, regarding motor stroke, we are developing a mechanistic "concept-driven" approach. The functional clinical impact of motor stroke depends on the location and extent of the ischemic/hemorrhagic lesion, but also on the existence of previous plastic changes in motor

cortical representation that can either limit or enhance the clinical consequences of stroke. Our objective is to study the functional maps of motor cortical representation by using navigated TMS in patients with risk factor of stroke (carotid stenosis, sickle cell disease,…). Data will be compared to age- and gender-matched normal subjects and the same investigation will be also performed in stroke patients at different phases and stages of clinical recovery. Thus, we will be able to determine functional correlations between cortical maps and motor performance, and also to distinguish between adaptive and maladaptive plasticity. Our results may have major impact on understanding the mechanisms underlying the clinical consequences of motor stroke through analyses of the plasticity of the motor cortex. This research will benefit from the recruitment of two M2 or PhD students, involved in neurovascular research, planned this year.

Other comments:

Regarding the validity of our neurophysiological measures as biomarkers, it is well established, and we have published numerous articles using these measures, e.g., cortical and peripheral nerve excitability parameters, as objective indicators of biological condition or state in pathophysiological or therapeutic follow-up studies.

Regarding funding and interaction with biotech companies, they are not "incipient", but instead we have large funding and clear interaction with several pharmacological and biotech companies, especially interested in our specific expertise on neurophysiological biomarkers (e.g., Biogen Idec, CSL Behring, Geneuro, LFB,…).

Team 11: Pathophysiology and pharmacology of coronary disease and cardiac failure

Team leader: Mr Bijan Ghaleh

We appreciate the analysis performed by the AERES committee and ensuing comments. We fully agree with the weaknesses/threats noticed in the report and corresponding recommendations.

Cohesion within the team and the consequences of having to separate places

We totally agree that although having 2 separate labs, one within Creteil Medical School and one in Alfort Veterinary School (ENVA) is a great opportunity but it might also represents a threat. As pointed out by the AERES committee, it is our intention to increase the number of regular meetings (whole team meetings, projects oriented meetings, etc) to improve the interaction between both labs. Importantly, it should be noticed that numerous projects mentioned in the proposal already involve the participation of both labs, *e.g.*, tissues or cells issued from animal models developed in ENVA are investigated in Creteil Medical School (10 min driving), therefore participating to the global cohesion of the team through these projects. Although in our mind these two geographycally separated labs are indeed one unique team, its cohesion is an important point for which members of the team are fully aware and are willing to permanently improve from one mandate to another one.

Weak expertise in molecular biology, policy to recruit scientists with strong skills in molecular biology and cell biology

Since at least two and half decades, our team is highly involved in the development and investigation of small and large animal models of cardiovascular diseases. Our skill in this area of research is well recognized as mentioned by the AERES committee. During the last years, we developed original cellular (isolated cardiomyocytes), biochemical (transcriptomic, protein expression, etc) and especially mitochondrial investigations but, as pointed by the AERES committee, we need to pursue the development of these molecular and cellular techniques. For this purpose we plan to further welcome post-docs previously trained in these areas and we recently obtained a grant from UPEC to welcome such a post-doc student (starting 1st September 2014). Finally, like in every research team, our ultimate goal is to be able to attract young scientists that can be recruited as permanent researcher, although this is very competitive.

Team 12: Pathophysiology of COPD and other respiratory consequences of environmental particles inhalation

Team leader: Mr Jorge Boczkowski and Ms Sophie Lanone

The Committee considers that our team and its project are excellent with a very innovative developing strategy. We would like to thank the Committee for this positive opinion and strong support to our project. As mentioned by the Committee, the ongoing collaborations with Serge Adnot's team, particularly on the topic of the relationships between pollution and senescence, but also with Roberto Motterlini's team (on CO-releasing molecules) will bring added value to our research.

We fully agree with the Committee that Sophie Lanone, one of the two team-leaders, will have to quickly qualify for a research director (DR2) position, to help her developing her leadership in the field of nanoparticles-induced respiratory diseases. She was actually in first position in the complimentary list at Inserm CSS4 last year and, as her CV did improve since, we hope she will qualify this year.

Team 13: Role of cell senescence in pulmonary and cardiovascular diseases

Team leader: Mr Serge Adnot

We would like to thank the Committee for the positive evaluation of our research activity and for the fruitful analysis of our 5-year research program. We thank the Committee for having outlined the new orientation of our research area, i.e. senescence. Indeed we have capitalized on our expertise on pulmonary hypertension to explore senescence cell as new avenues in terms of pathophysiology and potential innovative therapy in lung diseases. This is aligned with both our basic and clinical research interest in premature ageing in chronic diseases (lung, cardiac and blood) as expressed in the DHU A-TVB (coordinated by G Derumeaux and S Adnot) in which our team is strongly involved.

We fully agree with this committee's comment and one priority of our group will be to recruit young full time scientists. This will be achieved soon by recruiting a young scientist, Gabor Czibik, who will share his expertise on cellular biology with R Motterlini and J Boczkowski teams and will focus on the mitochondrial function consequences of cell senescence. Also we have talented young scientists in the team as A Houssaini, who is starting a postdoc abroad, and who will apply for a CR2 position when back to France within the next two years. Furthermore to expand the biological expertise within the team, we plan to recruit L Lipskaia, an expert in smooth and cardiac muscle cell biology, who recently joined the team with a position of associate Professor, and who will apply next year for a position of INSERM CR1 or DR.

We succeeded recently in attracting two senior researchers in cardiology, T Damy in 2010 and G Derumeaux in 2013 (co-coordinator of the DHU), who decided to join the team in order to extend the concept of cell senescence to cardiac disorders. One priority of these researchers is therefore to share and reinforce their expertise in the field of cardiovascular diseases with cell senescence, both at the basic and translational level, in order to apply it to cardiovascular diseases. We will extend the inter-team integrated research by developing collaborations within the IMRB teams and more specifically with R Motterlini's team (mitochondrial dysfunction within cell senescence process), J Boczkowski's team (environmental factors), B Galeh's team (cardioprotection in ageing), F Noizat-Pirenne's team (premature senscence in SCD), Y Levy's team (immunological clearance of senescent cells and vaccine response in COPD).

Team 14: Biomechanics & Respiratory apparatus: A multi-scale approach

Team leader: Mr Bruno Louis and Mr Marcel Filoche

We are highly grateful to the expert committee members for their evaluation of the team. We completely agree with the different points developed in the analysis of the committee.

Concerning the recommendations, we are aware that we have to increase the recruitment of young scientists. The recruitment of young scientists issued from the clinical field would be relatively straightforward. We have already identified two young researchers from the departments of B. Fauroux and A. Coste. The most challenging point will concern the recruitment of young scientists issued from the field of engineering sciences. The recruitment of a full time researcher (CNRS or INSERM) is indeed our priority for the next five years. Increasing internationalization through joint research is also one of our aims. We already initiated a collaboration with J. Grotberg from University of Michigan on surfactant and mucociliary clearance. At the same time we established contacts with the F. Nédélec group at Cell Biology and Biophysics unit at European Molecular Biology Laboratory (Heidelberg) in order to model the 3D cilia motion taking into account the detailed biophysical properties of microtubules and motor proteins. Our group has a long history of collaboration with industry and we want to maintain and extend this type of collaboration. Recently (April 2014), the group obtained a CIFRE convention with "Bertin Technologies". Then, we want also to continue to interact with the other teams of IMRB. From this point of view, the next collaboration will concern the mechanical properties of red blood cells with the team of F. Noizat-Pirenne.

Team 15: Molecular and genetic bases of CFTR and surfactant metabolism dysfunctions

Team leader: Ms Pascale Fanen

We would like to thank the AERES committee for providing constructing feedback about our research group. Please find below a short reply to some issues that were raised in the evaluation report.

We are currently developing inter-group (IMRB) integrated research. Actually, the emergence of the PhyDeS department has significantly increased inter-group communication, particularly on the topic of inflammation. As an example, we will test anti-inflammatory compounds developed by Roberto Motterlini on our CF models (*in vivo* and *in vitro*). We feel that the grouping of all the PhyDeS teams in the same building will further boost these interactions, since our team is located in Henri Mondor Hospital and the majority of the other teams are located in the Faculty of Medicine.

We agree with the committee that hiring new staff will be important in the close future and as mentioned in our SWOT analysis, we have recently recruited one fulltime INSERM researcher (A Hinzpeter, CR1) and one post-doc will apply to the competitive recruitment at INSERM as a research associate.

Addressing concerns of the committee regarding the involvement of the team in international network and collaborations and the low level of internationalization, we provide the following information, which was absent in the written document:

- We are currently applying to the 6th joint call for European research projects on rare diseases (E-rare) as a research partner, the first round of our application is successful and we are invited to submit a full proposal.
- We have a longstanding collaboration with the group of Jeff Whitsett and Tim Weaver, Cincinnati Children Hospital, USA, who is one of the world-leading group in the surfactant field and one PhD student (MD-PhD) will join his team during the next year (funding obtained).
- The leader and members of the future team have been invited to deliver lectures in recognized international meetings (i.e. Symposium at the 28th Annual North American Cystic Fibrosis Conference, October 10th 2014).
- We are involved (Ralph Epaud) in the European Management Platform for Childhood Interstitial Lung Disease (chILD-EU) project coordinated by M Griese, which is currently comprised of 10 academic partners from 5 European countries.

Lastly, in the written report we may not be have been clear enough regarding the workforce put in each axis and the number of persons involved. However, each axis is clearly conducted by one PI together with one PhD student and one Master student or one post-doc. The team member having also platform duties shares his time between the projects in which he is involved and the platform, as indicated in the list of staff members. As recommended by the committee, we will take advantage of the year 2014 to prioritize carefully the projects (transcriptomics and identification of interacting partners of SFTPC and CFTR) in order to focus on the most promising approaches and to increase our competitiveness.

In conclusion, we hope that these answers will comfort the committee about our capacity to develop successfully our project for the next 5 years.

Team 16: Morphogenesis and molecular genetics

Team leader: Ms Sylvie Dufour

The team would like to thank the Committee for its positive assessment of the scientific achievements and of the strategy and 5-years project.

The Committee raises the point of the challenging aspect in performing biomechanical “force measurement” experiments, and the currently little data available on the biomechanical properties of the gut and/or enteric NCC, particularly at a tissue or in vivo level. Recently, (after the visit of the committee), members of the team carried out few biomechanical assays in collaboration with physicists (Laboratory MSC, University Paris-Diderot) to probe embryonic avian gut using several techniques like tonometer, atomic force microscopy and micromechanical uniaxial stretching. The results provided evidence of the feasibility of such measurements of gut mechanical properties. As mentioned in the report of the Committee about the team project there are few if any groups equipped as the team and its collaborators to address this issue. The team believes it will be strength here to be able to provide to the scientific community the missing data about the gut tissue and enteric NCC biomechanical properties.

We agree that more technical staff will help supporting our projects. The reduced number of permanent technical staff of teams is a problem due to strong reduction in creation of such positions devoted to teams in benefit to platform-dedicated positions. However, the team has two permanent technical/engineer positions at 100% and one at 50%. In addition, several aspects of the team project will require the use of platforms and the team will benefit from the policy of the Centre to distribute technical manpower to these structures. Finally, to strengthen our technical staff, we use to request funding for technician or assistant engineer in grant applications but we will greatly appreciated help from the managing bodies in reinforcing our technical staff.

The team is working with UPEC in order to renovate the premises to host the team.

The committee “recommands to develop common team projects versus individual PI projects”. The team wants to point out that among the 3 axes of the project proposed, the second one is a common team project. The team believes that the data obtained from the other axes will rapidly allow developing common team projects in the near future.

Increasing the team international visibility and attractiveness is one of the team goals. Team members have been invited recently to several international meetings and have hosted PhD and postdocs from foreign countries. They have established numerous collaborations with laboratories of various countries in Europe, in Asia, Australia and United States. They aim at strengthening them and developing new ones, which will help in participating the international calls and networking.

Team 17: Transfusion and red blood cell (RBC) disease

Team leader: Ms France Noizat-Pirenne

We appreciate the global nature of the comments from the Aeres committee. As observed by the committee, the central theme on sickle cell disease and transfusion is well defined and scientifically sound. We have the intention to further refine the other projects of the new group, especially the genetic theme and, as suggested by the committee, to include aspects of bioinformatics. Our genetic studies are planned at 2 levels: firstly, an international collaborative level in which we provide DNA samples of fully documented patients for different conditions that we aim to study. This is the case for the Gen-Mod cohort, with the Boston Children's Hospital. It is also the case with our cohort of SCD patients (SCDTRANSFU) with transfusion reactions, as we collaborate with the Sanquin Institute in the Netherlands and the NIH in the US. Also, these collaborations will help to provide conclusive genetic results, as our cohorts will be combined with those of our collaborators. The second level is the local level within the IMRB. These developments depend on the access to the new NGS platform of the IMRB, which should be effective in a few months, and on the new organization of the genetic laboratory of the Henri Mondor Hospital. However, we are very optimistic about interesting developments and obtaining valuable information, based on all the local expertise and forces that we can rely on.

The arrival on site of the team of Michael Marden is a great opportunity for our new team and for the continuous development of our research on red blood cell and sickle cell disease. The administration of the Paris Est University (UPEC) has confirmed that the common laboratory will be ready on time (no later than January 2015). More fundamental approaches of polymerisation of HbS and introduction of oxidative stress will be possible. Common to sickle cell disease and thalassemias, an "over" exposure to free globins and subsequently unbound heme is also a pathway to be studied for understanding oxidative stress. Collaborative research works between members at the Henri Mondor and Kremlin Bicêtre sites are already ongoing, and all members of the new team meet every 2 weeks in lab meetings.

We do agree that neuroglobin and cytoglobin have a lower priority, but we currently maintain a database of globin structure/function which includes the redox properties: this is where neuroglobin, a protein discovered in silico via the genome, fits in as a model system within the bioinformatics planning.

Finally, we would like to mention that the former EFS team will be a new partner team in the Laboratory of Excellence GR-EX, allowing the development of other collaborations with high levels teams related to red blood cell research. The Bicêtre (M Marden) team is already part of this Labex.

Team 18: Drug discovery and cell therapy in cardiovascular disease

Team leader: Mr Roberto Motterlini

The team of Roberto Motterlini would like to thank the committee for their extremely positive assessment on the unit's achievements and acquired reputation as well as for considering our 5-year research strategy highly innovative. The committee has also greatly appreciated our plan to take advantage of Dr. Rodriguez's expertise and her proficiency in stem cell biology. Below is our reply to their specific comments and recommendations:

1) *There is a need to extend collaborations with private partners for improving the development of novel CO-releasing molecules.* We fully agree with this recommendation which is exactly in line with our current strategic approach. Indeed, since June 2013 we have been collaborating constructively with SATT IdF Innov for filing a patent on our novel CO-releasing molecules (hybrid CO-RMs) and the preparation of a proof-of-principle project. We are pleased to inform the committee that on the 21st of March 2014 we filed our first patent on the use of hybrid CO-RMs in the treatment of inflammatory and cardiovascular diseases. In addition, on the 26th of March 2014 the investment committee of SATT IdF Innov approved our research strategy and agreed to fund a proof-of-principle project on the anti-inflammatory action of hybrid CO-RMs for two years. The contract with SATT IdF Innov will clearly open a concrete opportunity for a business development plan and extend our collaborations to private partners interested in our technology. We would like to point out that the PI of the Team (Roberto Motterlini) has already a proven experience in technology transfer having been in the past founder, scientific director and member of the board of directors of the spin-off hemoCORM.

2) *The team has to recruit scientists with strong competences in cell biology of cardiac and inflammatory cells.* We agree with this recommendation although we would like to point out that both Dr. Motterlini and Dr. Foresti have more than a 20 years experience on the cellular oxidative stress response in cardiac and inflammatory cells. Moreover, as highlighted in the AERES report, our team is taking advantage of the expertise brought in by Dr. Anne Marie Rodriguez, who has many years of experience in cell biology and immunology. Concerning the implementation of more *in vivo* models, we are fully aware that this aspect has to be developed in our group and we had indeed recognized this limitation in our initial project submitted to AERES. The reason for this was primarily due to our recent move to France from abroad (January 2012) and the time necessary for writing grants and obtaining funds. We are pleased to inform the committee that thanks to an ANR grant and the SATT Innovation investment we are now able to recruit two post-docs who will be fully dedicated to develop the *in vivo* inflammatory models necessary to complement our *in vitro* studies. In addition, it is important to point out that we have already established within INSERM U955 solid collaborations with other teams in PhyDes department (Jorge Boczkowski and Serge Adnot) to investigate the potential therapeutic properties of our molecules in different *in vivo* models of diseases.

3) Establishing collaborations with groups expert in cardiac diseases and inflammation needs to be integrated in the policy of the team. We fully agree with this recommendation which is exactly in line with our past and current strategies. Indeed, since the initial discovery of CO-RMs in 2002 we have adopted a collaborative approach and gradually established a strong network of scientists working constructively with us. This is evidenced by the record of publications of the PI of the team (Roberto Motterlini) with French and International collaborators also working on cardiac disease and inflammation (see publications with R. Neviere and M. D'Amico). Moreover, we have recently submitted a project within a Horizon 2020 program coordinated by Prof G Derumeaux (Serge Adnot team) on cardiomyopathy and aging. This project includes several European and US collaborators with expertise in

cardiac diseases and inflammation. A full list of collaborators can also be found in the original project submitted to the AERES.

Jorge Boczkowski
Project carrier

Luc Hittinger
President of UPEC

EnvA
École nationale vétérinaire d'Alfort

Ministère de l'Agriculture, de l'Agroalimentaire et de la Forêt

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Maisons-Alfort, le 28 avril 2014

Objet : **S2PUR150008569 - INSTITUT MONDOR DE RECHERCHE BIOMEDICALE - 0941111X**

Madame, Monsieur,

En tant que Directeur de l'EnvA, je souhaite préciser que nous n'avons pas d'élément complémentaire à ceux déjà apportés par l'UPEC (tutelle principale), à propos du rapport d'évaluation de l'Unité "Institut Mondor de Recherche Biomédicale".

En vous remerciant, je vous prie de croire, Madame, Monsieur, en l'expression de mes salutations très distinguées.

Le Directeur,
Professeur Marc Gogny