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

Department for the evaluation of research units

AERES report on unit:

Institut Cochin

Under the supervision of the following institutions and research bodies:

Université Paris Descartes

Institut national de la santé et de la recherche médicale

Centre National de la Recherche Scientifique

January 2013

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

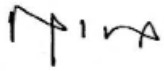
Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head



Pierre Glaudes

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

Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).

This score (A+, A, B, C) concerned each of the six criteria defined by the AERES.

NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

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

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

- Grading table of the unit: Institut Cochin

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

- Grading table of the team: Genomics and Signaling of Endocrine Tumors

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

- Grading table of the team: Mitochondria, Bioenergetics, Metabolism and Signaling

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

- Grading table of the team: Functional Pharmacology and Pathophysiology

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

- Grading table of the team: Immunology of Diabetes

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

- Grading table of the team: Receptor Signaling and Molecular Scaffolds

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

- Grading table of the team: Insulin and Glucose signaling, glucotoxicity

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

- Grading table of the team: Control of Pancreatic Endocrine Cell Development

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

- Grading table of the team: Iron, Oxygen and Energy Sensing in Pathophysiology

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

- Grading table of the team: Oxidative stress, cell proliferation and inflammation

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

- Grading table of the team: Stem cell environment and skeletal muscle homeostasis

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

- Grading table of the team: Genetics pathophysiology of intellectual disability and neurodevelopmental disorders

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

- Grading table of the team: Cell cycle and Liver pathophysiology

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

- Grading table of the team: Genetics, development and physiopathology of skeletal muscle

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

- Grading table of the team: Study of normal and pathological hematopoiesis

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

- Grading table of the team: Oncogenesis of digestive epithelia

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

- Grading table of the team: Gene expression, Development and Disease

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

- Grading table of the team: Genomics, Epigenetics and Pathophysiology of reproduction

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

- Grading table of the team: Virus intracellular trafficking

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

- Grading table of the team: Host-virus interactions

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

- Grading table of the team: Mucosal Entry of HIV and Mucosal Immunity

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

- Grading table of the team: Vascular Cell Biology in Infection, Inflammation and Cancer

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

- Grading table of the team: Cytokines and viral infections

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

- Grading table of the team: Innate immunity, toll-like receptors and variability of the inflammatory response

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

- Grading table of the team: Dynamics of T-cell interactions

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

- Grading table of the team: Dendritic cell physiology

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

- Grading table of the team: Comparative cell biology of host-apicomplex interactions

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

- Grading table of the team: Regulation of T-cell effector functions: from basic research to cancer

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

- Grading table of the team: Biology of Phagocytes

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

- Grading table of the team: Retroviruses, quiescence and proliferation

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

- Grading table of the team: Barriers and pathogens

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

- Grading table of the team: Neutrophils and Vasculitis

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

Evaluation report

Unit name:	Institut Cochin
Unit acronym:	
Label requested:	UMR INSERM, CNRS, Université Paris Descartes
Present no.:	U1016, UMR8104, UMR S_1016
Name of Director (2012-2013):	Mr Pierre-Olivier COURAUD
Name of Project Leader (2014-2018):	Mr Pierre-Olivier COURAUD

Expert committee members

Chair:	Mr Jacques SAMARUT, ENS Lyon
Experts:	Mr Matias AVILA, University of Navarra, Spain
	Mr Fernando ARENZANA-SEISDEDOS, Pasteur Institute, Paris
	Mr Mohamed BENAHMED, University of Nice Sophia-Antipolis
	Mr Walter BIRCHMEIER, University of Berlin, Germany
	Ms Dominique BONNET, Cancer Research UK, London, UK
	Mr Marc BONNEVILLE, University of Nantes (CoNRS representative)
	Mr Serge BOTTARI, University of Grenoble (INSERM CSS representative)
	Mr Ermanno CANDOLFI, University of Strasbourg
	Mr Carles CANTÓ, Nestlé, lausanne, Switzerland
	Mr Carlo CHIZZOLINI, University of Geneva, Switzerland
	Mr Lluis Fajas COLL, University of Lausanne, Switzerland
	Ms Cecile Denis, University of Paris 11
	Mr Jorge FERRER, University of Barcelona, Spain
	Ms Sylvie GUERDER, University Paul Sabatier, Toulouse

Mr Eric GILSON, University of Nice Sophia-Antipolis

Mr Andre M. GOFFINET, University of Louvain, Belgium

Mr Hai-Tao HE, University of Marseille

Mr Pedro Luis Herrera MERINO, University of Geneva, Switzerland

Mr Camille LOCHT, Pasteur Institute, Lille

Mr Martin J. LOHSE, University of Würzburg, Germany

Mr Paul MANGEAT, University of Montpellier

Mr Richard H. MORIGGL, University of Vienna, Austria

Mr Felice Petraglia, University of Siena, Italy

Mr Bruno QUESNEL, University of Lille (CNU representative)

Mr Thierry ROGER, University of Lausanne, Switzerland

Mr Philippe RONDARD, University of Montpellier

Mr Quentin SATTENTAU, University of Oxford, UK

Mr Laurent SCHAEFFER, University of Lyon

Ms Jaswinder K. SETHI, University of cambridge, UK

Ms Dominique SIGAUDO-ROUSSEL, University of Lyon

Ms Nathalie VERGNOLLE, University Paul Sabatier, Toulouse

Mr Kay-Dietrich WAGNER, University of Nice Sophia-Antipolis

Mr Peter S. ZAMMIT, King's College London, UK

Mr Antonio ZORZANO, University of Barcelona, Spain

Scientific delegate representing the AERES:

Mr. Jean ROSENBAUM

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

Mr Frédéric DARDEL, University Paris Descartes

Mr Paul-Henri ROMÉO, INSERM

Mr Stanislas TOMAVO, CNRS

1 • Introduction

History and geographical location of the unit

The Cochin Institute is in France one of the largest research units (laboratories). It carries on research aimed at deciphering molecular mechanisms of human physiopathology in the broad fields of endocrinology and metabolism, development and cancer, immunology and infection. The investigating approaches include basic research on several experimental models as well as clinical research with strong translational developments.

The Institute is affiliated to INSERM, CNRS and Université Paris Descartes. At the moment it encloses nearly 680 staff members including scientists from CNRS and INSERM (122), clinician scientists (77) from Université Paris Descartes and Assistance Publique/Hopitaux de Paris (AP/HP), research assistants under permanent position (155), post-docs (65), non-permanent technical staff (35) and PhD students (112) together with a few undergraduate students and short-term fellows. These people are working within 32 research teams.

The Institute was created in 2002, and renewed under the current affiliations in 2006 and 2010.

Following the last evaluation in 2009 major changes have been brought to the organization and governance of the Institute. The number of departments has been reduced from 6 to 3, together with the number of teams from 43 to the current number. This reduction in number of teams resulted from the departure and closure of a few groups and the merging of other groups following recommendation of the previous evaluation committee.

The teams are now dispatched within three departments corresponding to three major thematic axes:

- Endocrinology, Metabolism and Diabetes (EMD),

- Development Reproduction and Cancer (DRC),

- Infection, Immunity and Inflammation (3I).

The Cochin Institute is located on one unique campus and split over 4 buildings, and soon a 5th one, belonging to AP/HP, Université Paris Descartes and INSERM respectively. All these buildings are not directly connected but located within walking distance from each other.

Management team

The direction of the Institute has been undertaken by Mr Pierre Olivier COURAUD, assisted by a deputy director who will retire in 2016. The present director is candidate for the next term and will be helped by a deputy director and a head of core facilities. The Executive Board includes the director and deputy director, the head of core facilities and the head of clinical affairs.

The governance is completed by the Board of directors made of the executive board members and the directors and deputy directors of the three departments. This Board of directors meets once a month.

In 2011 the direction of the Institute created an International Scientific Advisory Board (SAB). This board is made of 11 members three of whom are foreign scientists. Since its creation this SAB met only once in December 2011 and endorsed the present project of the Institute for the 2014-2018- term.

AERES nomenclature :

SVE1_LS1; SVE1_LS3; SVE1_LS4; SVE1_LS6

Unit workforce

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	80	87	87
N2: Permanent researchers from Institutions and similar positions	122	129	129
N3: Other permanent staff (without research duties)	135	140	
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	7	7	
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	85	90	90
N6: Other contractual staff (without research duties)	45	45	
TOTAL N1 to N6	**474**	**498**	**306**

Percentage of producers	*100 %*

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	120	
Theses defended	141	
Postdoctoral students having spent at least 12 months in the unit*	95	
Number of Research Supervisor Qualifications (HDR) taken	19	
Qualified research supervisors (with an HDR) or similar positions	133	142

2 • Assessment of the unit

Strengths and opportunities

Major strengths:

- Several teams implementing high quality research and well recognized in their respective fields,
- Strong support of national research agencies, université Paris Descartes and AP-HP,
- Close association to a hospital,
- Strong translational efficiency,
- Diversity of biomodels,
- Efficient and up-to-date core facilities,
- Heavy support of research assistant staff,
- Efficient grant funding.

Opportunities:

- Localisation in Paris,
- Laboratory space available early 2014,
- Adjunction of performing teams already established.

Weaknesses and threats

Weaknesses:

- Poor renewal of the teams,
- Limited available current space,
- Limited animal housing facility,
- Few emerging young groups,
- Low attractive internal means.

Threats:

- Uncontrolled internal growth of the teams,
- Low attractivity to young leaders,
- Limited renewal of the groups.

Recommendations

Based on the great research potential and quality of the Institute the committee considers that the numbers of ERC applicants and awardees is too low. The committee strongly recommends to the direction of the Cochin Institute to have a much more willful policy to incite several young scientists and team leaders to apply to ERC grants.

The committee considers that the Cochin Institute as a whole lacks major international impact. The committee recommends that the Cochin Institute creates some international scientific events like an annual colloquium and/or summer schools.

The committee is wondering whether the internal translation office, which is managed by a single person, will be sufficient to manage an increasing demand. The role of this office will have to be probably redefined in regard to the newly created technology transfer business unit SATT (Société d'Accélération du Transfert de Technologiques) at the level of the IDEX consortium.

The committee strongly recommends to the Direction of the Cochin Institute to incite some teams to develop more integrated projects for a better visibility of the concerned teams.

The committee strongly recommends that the ERC as well as the further ATIPE/Avenir grants give rise to independent teams whose activity should be evaluated not earlier than 5 years after their creation.

The committee considers that the Institute should have a willfull policy for creating emerging groups from young talented scientists.

The committee strongly recommends that the Cochin Institute makes deep investments in animal housing in order not to hamper many ongoing competitive projects in the teams, and for the Institute to preserve its leading edge activity in the field of mouse experimental genetics.

The committee considers the Cochin Institute should have a long-term plan for its future development through the recruitment of young talented group leaders. The Institute should be careful about keeping some turnover and be vigilant about uncontrolled internal growth of the teams. Clearly some strong factors supporting attractiveness like laboratory space, human resources, dedicated funding, should be the immediate matter of planning to ensure the future development of the Institute.

3 • Detailed assessments

The scientific activity of the Institute relies upon a set of powerful and complementary core facilities dedicated respectively to genomics, proteomics, imaging (with divisions of photonic and electron microscopy), small animal imaging, mouse experimental genetics (including homologous recombination, embryo transfer and cryopreservation), morphological and histological analyses, cytometry and immunobiology, and animal housing. These facilities enclose up-to-date equipments and are managed by quite an important technical staff of 44 technicians and engineers. The core facilities represent then one major task force for developing leading edge technologies.

The total number of people directly involved in research activity including scientists, clinicians, research assistants, PhD and master students has increased only marginally during this last term from 565 in 2009 to 590 presently.

In 2012 two already established teams from other laboratories in Paris have joined the Cochin Institute coming from outside in Paris.

Assessment of scientific quality and outputs

The committee has been quite favorably impressed by major improvements in the research activity of the Cochin Institute during this last term.

The total number of publications has notably increased (324 in 2012 vs. 263 in 2009). This increase is higher than the increase in the number of scientists and clinicians meaning an overall increase in the productivity. The overall publication level has also improved with a number of publications in journal with IF>10 of 39 in 2012 as compared to 32 in 2009. As seen below from the individual assessments of the teams these improvements also apply for most of the teams.

In the same period of time the number of research grants has also considerably increased. As an example, the income from ANR grants has more than doubled. The increase is most evident for the EU grants whose incomes were multiplied by more than 4. This last point has to be noticed as it is currently rather uncommon in French research laboratories at this time. Also notably is the increase in clinical grants (PHRC) and grants with industry.

In total this has led to an overall increase, during these last three years, of more than 20% of the income, including salaries, for competitive grants.

Sixteen teams from all three departments are included into the recently labelled Labex programs of the Excellence Initiative, which is a clear sign of quality and recognition by local partners.

One starting ERC grant has been awarded in 2011 in the EMD department and two applications are pending. One team has been awarded an ATIPE/Avenir grant in 2012.

Since 2009 the Cochin Institute has filed 10 new patents and 8 international extensions of patents, which is a remarkable score and reflects the close links between fundamental and translational policy of the Institute.

The great involvement of numerous teams into clinical transfer is a hallmark of the Cochin Institute. This translational activity does not hamper the strategies of the groups to investigate in depth mechanistic aspects of biological phenomena. In some cases clinics is the driving force to address more fundamental issues. In other cases the transfer is the natural development of more basic investigations.

Assessment of the unit's academic reputation and appeal

Many researchers have a fairly strong international impact as being invited in international meetings as speakers, chairpersons, organisers (see individual assessments of the teams below) or as beeing leaders of international projects.

As mentioned above the Cochin Institute is member of the IDEX (Initiative of Excellence "Université Sorbone Paris Cité") that was launched as a national competition by the government in 2011. Sixteen teams of the Institute belong to 6 labeled projects of excellence (Labex) in collaboration with other teams from other institutions in Paris. The Cochin Institute has also been labeled as a National Integrated Site for Cancer Research (SIRIC) in partnership with the Georges Pompidou medical center and many teams are contributors to SIRIC projects. Similarly following national calls of 2011 and 2012 several teams of the Institute have been selected to belong to two University-Hospital Departments (DHU) in networking collaboration with other medical centers in Paris. One of these DHU includes all the teams of the EMD department. The other one includes 3 teams from the 3I departement.

At the international level the Cochin Institute has also developed many partnerships. Since 2009 the Institute is involved through its teams into 16 EU programs of several types among which 4 are led by members of the Institute.

It then appears that the Institute benefits from a great credit and recognition at the international level through several of its members and teams.

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

The committee has been impressed by the wide interest of most of the teams in translational activities, either toward clinical or industrial developments.

The close physical interactions between the Institute and the hospital together with the existence of a chair of medical affairs appointed to the executive board certainly contribute to development of this strong culture of clinical transfer.

Moreover, the intense translational activity is the consequence of the creation in 2009 of an internal office for technology transfer and to a strong networking between the Cochin Institute and the field of biotech and pharmaceutical industry. This strong transfer activity is also the result of some internal incentives like the "POC" programme aimed at supporting proofs of concepts. Indeed in 2012, 3 projects were funded out of 10 applications. The committee considered however that the financial support of each POC (15K€) is rather low and might be redundant with actions promoted by the newly created SATT. This budget could be reallocated to other actions eg. fostering internal collaborations or emergence of new teams. Nonetheless these supports allowed to identify a few highly promising translational projects which have been further supported at quite high levels by external translational business units (INSERM transfer, SATT) playing thereby a laudable leverage effect.

In addition to these actions the Institute started in 2012 an annual meeting (*Donny Strosberg Institut Cochin meeting*) hold in partnership with industrial partners for the presentation of projects and speed dating.

All these initiatives denote then a strong culture and efficiency in economic development from the research made at Cochin Institute.

In terms of social transfer it is to be noticed that several researchers, teachers and PhD students participate in interacting activities with the society through public debates and meetings and even more interestingly, through tutoring of scholars, in order to promote science among young generation.

Assessment of the unit's organisation and life

As mentioned above the structure of the Institut Cochin has been widely remodeled during recent years with reduction of the number of teams and of departments. It appears clearly the the departments were created to facilitate the overall management of the Institute. They have no independent strategic function and have no dedicated budget. Their role is to animate internal scientific life and to raise proposals and demands to the executive board for its strategic and decisional actions.

The affiliation of the teams to the departments was decided in agreement between the teams and the direction of the Institute. No team is contesting this distribution. The committee has no specific remark on the role and composition of the departments.

As mentioned above some current teams have been reorganized following the previous evaluation by merging two small teams. In some cases this merging has not led to implementation of a new integrated project within the team and the persistence of two sub-teams is still quite apparent, with, in some cases, two overt leaderships (see below the individual assessments).

The committee would strongly recommend to the Direction of the Cochin Institute to incite these teams to develop more integrated projects for a better visibility of the concerned teams.

Internal calls for proposals (PIC) have been launched annualy since 2009 to support emerging collaborative projects at a level of 15K€/project. This action generates collaborations between teams from different departments. Only 2 such PIC have been funded every year and this initiative would definitively deserve to be amplified. All these actions contributed to raise the number of publications resulting from internal collaborations from 12 in 2009 to more than 40 in 2012.

Beside this well considered strategy, the committee has some major concerns about the policy concerning the emerging young groups.

As mentioned above one starting ERC grant was awarded but the committee discovered that the young awarded group is still affiliated to its previous team. The committee considers this situation as totally abnormal with regards to the rules of ERC grant management. This situation results from apparent discordant statements or understandings between the previous evaluation committee, the CNRS and INSERM and the direction of the Institute. Indeed the previous evaluation committee made a statement, supported in that by CNRS and INSERM, recommending not to create small groups without non-permanent personnel. This statement might have been valid for already existing groups with limited fund raising activity and subthreshold critical mass of excellence, but should not apply to emerging highly selected groups led by talented scientists.

The Institut Cochin has recently included two highly-performing already established teams coming from other institutions (see below). Although this is a good sign of attractivity and enrichment the committee noticed that most of the other teams have been at the Institut Cochin for a long time.

The direction mentioned the launch of an international call to attract 2-3 group leaders in 2014-2015. The Institute will have to dedicate specific funds for this initiative and at a competitive level in regards to other european research institutions. The committee strongly supports this project and recommends that the direction of the Institute takes the proper initiatives to raise significant ressources to be attractive enough.

The lack of allocated research assistants to young groups was an issue raised by scientists. These human ressources are coming almost exclusively from INSERM and CNRS. In response to the committee both national agencies claimed that there is no restriction for allocating available ressources to individual groups rather than to common facilities, provided this is the priority of the direction of the Institute.

The committee was unanimous in acknowledging the whole of the core facilities as one strength of the Cochin Institute and recommends their further development in order to be kept at the best international standards. In that sense the committee had two major concerns. The first one is the insufficient manpower on the genomics facility mainly for genomic sequencing. The second, which is a major issue, is the critical need for animal housing. We learned from the Director that refurbishing of some current animal house facilities space is ongoing and that new space should be made available early 2014.

In terms of human ressources management it appeared from independent discussions the committee had with the scientists, post-docs, research assistants and students, that everybody is satisfied by the management of the Institute and happy to work at the Cochin Institute with a fairly good "*Institute spirit*". One request by the scientists is to create, within the human ressources management office, a service dedicated to the coaching of scientists and post-docs in terms of careers, mobility, training…

The scientific life of the Institute is quite intense with seminars, clubs dedicated to specific technological or scientific topics, annual retreats of the departments.

Assessment of the unit's involvement in training through research

The number of PhD students at the Cochin Institute has remained nearly constant during these last three years (~115-120) and the number of PhD defenses averages 28 per year.

In contrast the number of master students has considerably increased from 38 in 2008 to 60 presently. The training of these students within the teams is rather strong (see below the individual assessments of the teams).

Since 2008 the Institute has implemented a committee for tutoring PhD students which also takes care of master students and post-docs. This committee can make proposals to the Board of Directors. It also organises PhD annual meetings. A local association of young scientists (JeCCo) also contributes to the life of students and young scientists.

Besides teachers, more than 30 scientists of the Institute participate to teaching in PhD programs and Master programs and several of them and teachers are playing management role in these programs.

Although it was not always evident to discern, many of the PhDs who have been recently trained in the teams have found positions either as post-docs or as assistant professors in french and foreign institutions.

Therefore the committee considers that training activity of the Institute is quite good which certainly explains its attractiveness for Master and PhD students.

Assessment of the five-year plan and strategy

The aim of the Cochin Institute is to preserve its competitiveness and attractivity and its strong efficiency in translational research. In that way the Institute is creating a critical mass in the fields of diabetes and human virology, respectively, through the recrutement of already established groups.

The committee considers that the Cochin Institute should have a long-term plan for its future development through the recruitment of young talented group leaders. The Institute should be careful about keeping some turnover and be vigilant about uncontrolled internal growth of the teams. Clearly some strong factors supporting attractiveness like laboratory space, human resources, dedicated funding, should be the immediate matter of planning to ensure the future development of the Institute. The committee is confident that the Director is aware of this issue and has some prospects in that sense.

4 • Team-by-team analysis

Team 1 : Genomics and Signaling of Endocrine Tumors

Name of team leader: Mr Jerôme BERTHERAT

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2 (1.3)	3 (1.8)	3
N2: Permanent EPST or EPIC researchers and similar positions	5 (3.1)	5 (3.1)	5
N3: Other permanent staff (without research duties)	2	3	
N4: Other professors (PREM, ECC, etc.)	2 (0.2)	2 (0.2)	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		1	3
N6: Other contractual staff (without research duties)	1	1	
TOTAL N1 to N6	**12**	**15**	**11**

Percentage of producers	*100 %*

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	2	
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	6	8

• Detailed assessments

Assessment of scientific quality and outputs

The group builds on a long-term effort to understand the genetic basis of adrenal tumors. They produced a total number of 129 high-quality papers of which 60 are signed as last author. They link genetic defects in WNT and cAMP signaling pathways to adrenal tumors. Other studies include the role of such mutations in associated tumors, as well as efforts to use transcriptional profiling to classify adrenocortical tumors based on their molecular composition and clinical behavior. The studies have been largely published in J Clinical Endocrinoly and Metabolism, the most reputable journal in human endocrinology, and presented in commentaries or reviews in Lancet and Trends in Endocrinology. The team leader has been an important collaborator in a key study in Nature Genetics. Some of the studies are conventional clinical endocrinology studies with a molecular genetic component, whereas others exploit recent genetic findings to improve understanding of disease and patient care, or aim to identify novel defects or therapeutic targets.

Assessment of the team's academic reputation and appeal

The team leader and several members are regularly invited to the most reputable international workshops and congresses in their subspeciality as well as in Endocrinology in general. Two members have gained national prizes, and an award in UK. The team has had a prominent position in the organization of international meetings, review boards, and coordination of scientific and clinical research activities. Overall the team has a strong reputation in its field.

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

A scientist who is joining the team has a patent on a cell cycle regulator for cancer therapy. The team has implemented assays that have moved to the clinic locally.

Assessment of the team's organisation and life

Consistent with the aims and team composition.

Assessment of the team's involvement in training through research

Three PhD theses were completed during this period. Given the large number of senior members this number is not very high. The first two PhDs are working as assistant professors in French universities. The team has trained several master students. They have organized postgraduate training activities on endocrine tumors.

Assessment of the five-year plan and strategy

The team is already using whole genome sequencing to search for germ-line and somatic mutations genome-wide. They are also examining DNA methylation and will include miRNA studies genome-wide.

The approach makes perfect sense, and has the potential to reveal novel mechanisms and targets. There is a major challenge in that the team does not appear to have experience in handling whole genome sequence data or to perform complex integrative analysis of different omic datasets. The NGS (Next Generation Sequencing) strategy is now commonplace in other solid tumors, and they are ideally suited to initiate such studies given the unique collection of tumors and patients for these rare tumors, although they need to decide who will develop the expertise that will make this project succeed.

The second component of the project will attempt to unravel molecular targets underlying how cAMP and WNT signaling cascades defects in adrenal tumors cause altered growth and hormonal secretion. This will be primarily carried out in inducible models based on an adrenal cancer cell line, although they will also attempt to make primary tumor lines.

Finally, a new line will be developed to understand ERK and angiotensin signaling in differentiated thyroid tumors, a much more frequent disease.

Conclusion

- Strengths and opportunities:

This is a highly focused lab that has aquired a dominant position in the field of genetic basis of adrenal tumors. They have a unique collection of tumor samples as well as the expertise to make real progress in the discovery of molecular targets for future development of therapeutics and prognostic markers. The arrival of a senior researcher having a recognized expertise in cell signaling cascades, should allow the defects and functional consequences of the cAMP and Wnt cascades to be characterized.

- Weaknesses and threats:

There is a perceived need to develop stronger expertise in computational genomics/systems biology, or to team up with a collaborative team that has strong expertise and is willing to make full commitment to the analysis of their ongoing NGS data, rather than relying on support from bioinformatics platforms. Similarly, there is a need to develop exertise in cell biology, in particular with respect to the investigation of receptor-triggered signaling cascades (cf. cAMP and Wnt cascades).

PhD training record is not strong and can be improved.

- Recommendations:

Strong recommendation to develop stronger expertise in computational genomics/systems biology, or to team up with a collaborative team that has strong expertise and is willing to make full commitment to the analysis of their ongoing NGS data, rather than relying on support from bioinformatics platforms.

Team 2 : Mitochondria, Bioenergetics, Metabolism and Signaling

Name of team leader: Mr Frédéric BOUILLAUD

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	4 (3.1)	4 (3.1)	4
N2: Permanent EPST or EPIC researchers and similar positions	4 (2.7)	4 (2.7)	4
N3: Other permanent staff (without research duties)	4	4	
N4: Other professors (PREM, ECC, etc.)	1 (0.2)	1 (0.2)	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)			
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	13	13	8

Percentage of producers	*100,00 %*

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

• Detailed assessments

Assessment of scientific quality and outputs

The team of Mr Frédéric BOUILLAUD contributed to the concept that some mitochondrial components (UCP2, H2S, CPT1) are sensors of metabolic stress that direct the metabolic switch (glycolytic or oxidative) of the cell in order to accommodate to this stress. The originality of the research scope of the team relies on the study of 1) the role of CPT1 and UCP2 in the regulation of substrate oxidation in different pathophysiological situations (metabolic syndrome, cancer …) and 2) the integrated analysis of the diverse mitochondrial bioenergetic components in pathophysiology, with specific interest in human mitochondrial diseases.

One of the main results obtained these last years is that the mitochondrial CPT1 is a key target to increase mitochondrial fatty acid oxidation. Targeting liver and skeletal muscle CPT1 respectively improves insulin sensitivity in obese mice and protects muscle cells from lipitoxicity, which makes CPT1 regulation a therapeutic target. In addition they have shown that mitochondrial defects cause genetic diseases that had not previously been associated with mitochondria.

This team is the result of a recent merging among 3 prior teams. Certainly, they have a great potential in mitochondrial research thanks to their combined expertise. During the last 6 years (2007-12) they have published a large number of articles (91 original articles and 16 reviews). When taking into account the articles in which they are senior authors the number is still very significant: 35 (21 of them in the first quartile). As to quality, the number of original articles published as senior authors in high impact factors is more limited (only 1 article above IF 10 (Gastroenterology) and 7 in between IF 7-10) (Neurology, J Hepatol, Cell Mol Life Sci, PNAS, Aging Cell). Based on the expertise of the team more high impact publications would be expected.

Assessment of the team's academic reputation and appeal

The academic reputation of the team is high as measured by the participation in high impact factor journal articles as collaborators (5 articles above IF 10 (Cell Metab, Hepatology) and 8 in between IF 7-10) (Diabetes, Am J Hum Genet, Hum Molec Genet, PNAS, NAR, Neurology). They have been invited into a large number of national or international meetings. The project leaders are well known in the field of mitochondria research and participate in a number of national committees, including the French Academy of Sciences. Team members participate in numerous advisory committees and three members of the team were recipients of important French awards. They appear less attractive for recruitment of young scientists since there are no post-docs in the team.

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

Project leaders obtain part of their funding through collaboration with the industry (Boehringer-Ingelheim, Parfums Christian Dior, Servier, etc). In addition, 3 patent applications have been filed. They participated in the validation of enzymatic assays for clinical diagnosis in order to allow comparison of results between diagnostic centers (Medja et al., Mitochondrion 2009). These protocols are now used in most French diagnostic centres and abroad (Spain, Italy, South Africa…).

Assessment of the team's organisation and life

Consistent with the aims and composition of the team. Not applicable

Assessment of the team's involvement in training through research

During the 2007-12 period they had 15 PhD students in the team. 10 PhD thesis were succesfully defended and 5 thesis are in progress. Among the PhD who have defended, 4 are postdoc fellows in academic laboratories (Switzerland, Chili and France), 2 are project managers, and three are academic lecturers. All the team scientists are involved in teaching programs (PCEM1, Masters, Practical workshops, lectures).

Assessment of the five-year plan and strategy

The general goal is to study the crosstalk between mitochondrial function, metabolism and diseases by deciphering the molecular mechanisms involved in mitochondrial adaptation to intrinsic and/or environmental insults. The team proposes to further characterize human mitochondrial diseases in tight collaboration with the diagnostic center of mitochondrial diseases of La Salpêtrière to set up novel diagnostic tools and to determine the bioenergetic and cellular consequences of homoplasmic mutations of the MT-ATP6 gene. The team will also continue to work on the metabolic reprogramming capacity of several cells and tissue to identify reliable biomarkers depending on stress condition.

The team has been recently founded and probably they need to mature their way to better address and solve relevant questions. This has been started already as several new projects are led by two senior researchers and should be pursued in order to focus on a limited number of selected and related topics.

Conclusion

- Strengths and opportunities:

Considering the expertise of the leaders in mitochondrial biology, and the relevance of mitochondrial dysfunction in human pathology, it is clear that this team has a great potential, which should be further developed. The three groups that now constitute the team have brought together complementary expertise that will render the analysis of mitochondrial function considerably more complete and accurate than before.

- Weaknesses and threats:

The team has too many project leaders and as a consequence the number of high impact factor articles published as senior authors is somewhat low. The role played by the many scientific collaborators in this team is not always clear, but this may be attributable to the recent merger of the 3 former teams. Low number of post-docs.

- Recommendations:

They should try to merge research lines to the ones that generate most synergy and provide the most novel and relevant concepts to be able to attract more PhD students and postdoctoral fellows. Synergy will come from a more focused project and a visible single leadership.

The number and level of publications should be improved in the coming years with the increased maturity of the group and the implementation of efforts.

The absence of postdoctoral fellows should be taken care of.

Team 3 : Functional Pharmacology and Pathophysiology

Name of team leader: Mr Ralf JOCKERS

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1	1	1
N2: Permanent EPST or EPIC researchers and similar positions	2 (1.3)	3 (2.3)	3
N3: Other permanent staff (without research duties)	1	1	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	3	3
N6: Other contractual staff (without research duties)	2	2	
TOTAL N1 to N6	**10**	**10**	**7**

Percentage of producers	*100 %*

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

• Detailed assessments

Assessment of scientific quality and outputs

The team focuses on the understanding of the function and therapeutic potential of membrane receptors. They are interested in the 'Molecular Pharmacology' and 'Endocrinology' of G protein-coupled receptors (GPCR) and cytokine receptors in metabolic diseases. They developed the characterization of two different families of membrane receptors, the melatonin (MT) and leptin receptors. The team leader is internationally recognized in the field of melatonin receptors, a G protein-coupled receptor (GPCR) involved in biological rhythms and energy homeostasis. The team has used the MT1 receptor to establish two proofs of concepts in the very competitive field of GPCRs, the major family of receptors in humans : (i) it has shown that GPCRs function can be regulated by heteromerization with orphan GPCRs; (ii) it has proposed the concept of asymmetric behavior in a GPCR dimer, where one protomer can be coupled to the G-protein whereas the second protomer interacts directly with a regulatory protein. In parallel, the team has developed the characterization of the leptin receptors by molecular pharmacology and cell biology approaches. Their work provides several new perspectives and a novel therapeutic concept for the treatment of obesity by targeting endospanins instead of classical leptin receptors. A major effort was dedicated to the development of new technologies (BRET, proteomic approaches, etc) and screening activities to identify and characterize innovative therapeutic targets.

Excellent level of publications with more than 50 articles from 2007 to 2012, and results are regularly published as senior authors in high-ranking journals (EMBO J, Nat Genetics, PNAS, Mol Cell Proteomics, Trends Pharmacol Sci).

Assessment of the team's academic reputation and appeal

The group leader is coordinator of one international network and one Korean-French screening project, and of one national ANR project. Since 2012 he is the founder and director of the French national network on GPCRs (« GPCR-Physio-Med ») which plays a very important role in organizing the French community interested in the GPCRs field. He organized one international meeting on this topic. He was chairman and discussion leader at Gordon and FASEB conferences. He is editor-in-chief of « Frontier in Cellular Endocrinology », invited member of Faculty of 1000 and he has reviewed a large number of manuscripts and grant applications. The team is attractive for foreign postdocs. The team leader is regularly invited to international GPCRs meetings including Gordon conferences (3), Keystone meetings (1) and FASEB conferences.

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

The group leader has a good competence and skill to develop contracts of collaboration or consulting with pharmaceutical and biotech companies, and two patents were issued. Due to the publication of articles with potential interest in medicine, the group leader gave interviews in national magazines and newpapers, in addition to radio station interviews. The team also participated in the training of pupils from secondary schools ("Apprentis chercheurs" program of the Institut Cochin).

Assessment of the team's organisation and life

In accordance with the goals of the team.

Assessment of the team's involvement in training through research

The team has trained five PhD students (3 are in progress). The two PhDs who have defended are now postdoc fellows in academic laboratories (France and Belgium). Two permanent researchers organize a Master 2 module. The group leader has organized several national workshops, in particular on BRET technologies, and he regularly participates in international and national training courses for researchers, PhD and Master students.

Assessment of the five-year plan and strategy

The group will continue to work on the molecular pharmacology and cell biology of MT and leptin receptors. The team now wants to develop the physiological study of MT, GPR50 and leptin receptors, in order to propose innovative and personalized therapeutic strategies in the field of obesity and diabetes. The team proposes to further characterize GPCR heteromers involving MT receptors in both in vitro and in vivo studies in collaboration, and to screen for heterodimer-specific compounds. Functional role of GPR50 in energy homeostasis will be studied in knock-in and knock-out mice already in preparation. The team is also strongly involved in the development of drugs that target leptin receptors for body weight control. The team will keep a similar organization with the group leader in charge of the MT and GPR50 receptors projects, whereas a permanent researcher will be responsible for the program on leptin receptors. The human resources, fundings and collaborations are in good coherence with the research plan.

Conclusion

- Strengths and opportunities:

The team makes a real effort to push their research projects from the molecular pharmacology to the physiological level with the development of transgenic mice and drugs. Very strong leadership of the group leader : very active in developing research projects, obtaining grants, organizing national and international networks and collaborations, setting up of collaborations with private companies. The team is attractive for foreign postdocs. Regular publications in high impact factor journals.

- Weaknesses and threats:

Only few specific weaknesses and threats were identified. The team was able to perform hit validation of drugs, but it is currently unable to perform hit optimization, an obligatory step for patent filing and negociation with industrial partners. In addition, the group leader should receive more support from the other permanent researchers in the team that should take over research programs more independently.

- Recommendations:

This is an excellent group with a high level of international recognition and good grant support. The quality and originality of the past and future projects is very good. More leadership is expected from other permanent researchers in the team.

Team 4 : Immunology of Diabetes

Name of team leader: Ms Agnès LEHUEN and Mr Roberto MALLONE

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	4 (3)	4 (3)	4
N2: Permanent EPST or EPIC researchers and similar positions	2 (1.5)	3 (2)	3
N3: Other permanent staff (without research duties)	6	3	
N4: Other professors (PREM, ECC, etc.)	1	1	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	6	5	5
N6: Other contractual staff (without research duties)	7 (6)	7 (6)	
TOTAL N1 to N6	**26**	**23**	**12**

Percentage of producers	***100 %***

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	5	
Theses defended	10	
Postdoctoral students having spent at least 12 months in the unit	5	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	7	7

• Detailed assessments

Assessment of scientific quality and outputs

The team plans to join the Cochin Institute in 2014 and integrate the Department of "Endocrinology, Metabolism, Diabetes". The objective is to create a new research center in diabetes and metabolism with the largest diabetes clinical department in Paris. This team has a long-standing research activity in the field of type 1 diabetes (T1D). They address fundamental as well as clinical questions about the initial events associated with diabetes development and has also strong translational activities. Major findings include the demonstration that NKT cells contribute to T1D development. In the past years they published these results in high impact journals (Immunity, J Exp Med). In a more recent study the group uncovered unsuspected interactions between B1a B cells, Neutrophils and pDC plasmacytoid dendritic cells that initiate an inflammatory loop in the pancreas which will subsequently promotes adaptive CD8 T cell response against islet antigens. This original observation opens a new perspective in the initial triggering events of T1D that will be further pursued. These different observations were reported in high impact journals (Nat Med, Immunity, JEM).

A second research activity of the team concerns the role of the adaptive immunity and mainly CD8 T cells in the development of T1D with a strong focus on developing diagnostic and therapeutic approaches to control this prime actor of T1D. An in vitro system that permits the characterization of circulating auto-reactive CD8 T cells from the blood of patients was developed and used to show that the autoreactive CD8 T cell repertoire evolves as disease progresses. Along the same line, the team is developing humanized mice with exclusive expression of class I or class II HLA. These unique mouse models will be essential tools for further therapeutic vaccine development. Finally the team uncovered a new molecular mimicry between M avium paratuberculosis and the ZnT8 islet antigen pointing to a new initiating event in T1D.

In summary this team has an excellent scientific production.

Assessment of the team's academic reputation and appeal

Excellent international recognition as evidenced by invitations to several international meetings (Keystone meeting, Gordon Conference, International Immunology meeting, International Congress of the Diabetes Society…), invitation to write reviews in excellent journals (Nat Immunol, Nat rev Immunol..).

Good attractiveness as evidenced by the recruitment of the "avenir" group, one CR2 researcher and several post-doctoral fellows.

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

Two patents from the team members have been granted and licensed. In addition there is a very good grant application activity with a high success in fund raising.

Assessment of the team's organisation and life

This is consistent with the development plan.

Assessment of the team's involvement in training through research

Strong implication in teaching with all researchers being either responsible or participant to several Master. Training of 5 M1, 6 M2 and 12 PhD students, 10 of which graduated.

Assessment of the five-year plan and strategy

The projects are, by and large, in direct continuation with the previous research activities of the team but new projects at the interface between immunology and metabolism will be also initiated. Furthermore a strong effort in translational research is proposed with the development of several approaches of immune monitoring and intervention strategies to predict and prevent T1D onset in humans. There is a very good integration of clinical, translational and fundamental research in type I diabetes.

Conclusion

- Strengths and opportunities:

The team has proven strong expertise in the proposed line of research. The relocation at the Cochin Institute will foster new interactions with both immunologists and members of the metabolism/endocrinology department. Furthermore the proximity with the clinical diabetes department should be extremely fruitful for the development of new perspective in translational research.

- Weaknesses and threats:

Some high-risk projects are proposed, with the generation of complex transgenic mice (T cell metabolism and T1D) or neonatal tolerance to insulin Specific stop and go strategies should be defined to ensure re-orientation of the project if needed.

Collaborative interactions between the team leaders are not apparent although their research themes are closely related.

- Recommendations:

Development of further interactions with the immunology department are welcome. The team members are very good experts in the field of type I diabetes, whereas their knowledge in type II diabetes is more limited because of a lack of skills in metabolic phenotyping. Concentrating their efforts on type I diabetes projects only should be considered.

Team 5 : Receptor Signaling and Molecular Scaffolds

Name of team leader: Mr Stefano MARULLO

Workforce

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

Percentage of producers	*100 %*

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	2	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

The team has focused on two main topics : beta-arrestin function and G protein-coupled receptors (GPCRs) maturation. Beta-arrestin-1 and -2 were originally described to be important for GPCR desensitization and internalization. During these processes, beta-arrestin-1 and -2 are recruited to the plasma membrane and they interact directly with the receptor. Over the years, further signaling functions of beta-arrestins have been identified. During the period 2007-2012, the team has obtained very important and innovative results on these highly competitive topics: (i) oligomeric beta-arrestin-2 shuttles from the cytosol to the nucleus where it interacts with proto-oncogene Mdm2; (ii) beta-arrestins also interact with the tumor supressor PTEN to negatively regulate cell proliferation; (iii) analysis of the trafficking of the chemokine GPCR CCR5, a co-receptor for the immunodeficience HIV virus, has shown that most of the neo-synthetized receptors are retained within intracellular compartments of human lymphocytes and monocytes; (iv) the bacteria meningococcus stimulates the beta-arrestin pathway of the GPCR beta-2 adrenergic receptor, allowing it to cross the brain vascular endothelium and penetrate into the meninges. Very good level of publications with more than 20 original articles from 2007 to 2012, and some published in high-ranking journals (Cell, EMBO J, PNAS, Blood, Trends Pharmacol Sci). Very good scientific production.

Assessment of the team's academic reputation and appeal

The team leader was invited to international GPCRs meetings including Gordon conferences (2) and Keystone meetings (1). The group leader was chairman in a Gordon Conference. One permanent researcher is joint coordinator in a Royal Society International Joint Project (University of Glasgow, UK). The team has hosted two foreign postdocs and two visiting professors (Canada, Mexico). The team is foreign member of the Canadian research academic group on drug discovery (GRUM/RQRM, Univ of Montréal), and of the national « laboratory of excellence » Labex « Who I am ».

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

One patent was issued, and two new licenses were obtained for previous patents. Team members have contributed to scientific popularization for a national cancer foundation and are tutoring secondary school students. Of note, the group leader has a lot of administrative responsabilities as Vice President for research and co-director of the PhD program of the University Paris Descartes.

Assessment of the team's organisation and life

The team is organized in a coherent manner according to the research program developed.

Assessment of the team's involvement in training through research

The team has trained five PhD students (1 is in progress). Among the PhD who have defended, three are postdoc fellows in academic laboratories (USA, Canada and France) and one works as project leader in a biotech company (Paris, France). The team leader is strongly active in the organization of teaching at the University Paris Descartes as Vice President for research of the University, co-director of one PhD program, organizer of the Master program in Cell biology and development. Two other permanent researchers in the team are organizers of a Cell signaling course for Master students, and Scientific english writing courses for PhD students.

Assessment of the five-year plan and strategy

The group will continue to work on the molecular mechanisms of receptors and beta-arrestins signaling using cell biology, biophysical and biochemical approaches. The most original and exciting project is to understand the molecular basis of the interaction between the cell surface GPCRs and infectious pathogens (meningococcus, plasmodium). Due to the evidence of the implication of beta-arrestins in an increasing number of physiological and pathophysiological processes, it is important that the team develops the investigation of the beta-arrestins and their implication in cell proliferation and cancer. The team will keep a similar organization with the group leader responsible for the projects on GPCRs trafficking and on the interactions between pathogens and GPCRs. The two other permanent researchers are in charge of projects on beta-arrestins trafficking and the implication in cell proliferation and cancer. The human resources, fundings and collaborations are in good coherence with the research plan.

Conclusion

- Strengths and opportunities:

Originality of the project to investigate the molecular basis of the interactions between GPCRs and pathogens. As beta-arrestins play key roles in cells, it is important to investigate their implications in the field of expertise of the team. The team has developed strong and productive collaborations. Experience of the team to publish in high impact journals. Permanent researchers are obtaining fundings independently of the team leader.

- Weaknesses and threats:

Very strong competition on the beta-arrestin projects. The group leader has strong and time-consuming administrative duties. It requires that the other permanent researchers in the team take over research programs more independently. The team has enough fundings for the period 2013-2015, but recently had difficulties in obtaining ANR national grants.

- Recommendations:

To pursue the ongoing projects and maintain the level of excellence in publications.

Team 6 : Insulin and Glucose signaling, glucotoxicity

Name of team leader: Ms Catherine POSTIC

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3	3	3
N2: Permanent EPST or EPIC researchers and similar positions	4 (3.8)	4	4
N3: Other permanent staff (without research duties)	2	2	
N4: Other professors (PREM, ECC, etc.)	1 (0.25)	1	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	4	4
N6: Other contractual staff (without research duties)	2	2	
TOTAL N1 to N6	16	16	11
Percentage of producers	*100 %*		

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	6	
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	5

• Detailed assessments

Assessment of scientific quality and outputs

This team has broadly focused on dissecting the molecular regulation of glucose metabolism and glucotoxicity. They aimed to uncover new potential targets for the treatment and/or prevention of hepatic steatosis, insulin resistance, and hyperglycemia. To achieve this they have focused on two highly relevant transcription factors (ChREBP and FoxO1), an inhibitor of insulin receptor catalytic activity (Grb14) and a new marker of hepatic steatosis, Adiponutrin/PNPLA3. In the last five years the team has made some important contributions in these area and they seem set to continue to significantly improve our understanding further. Particularly noteworthy discoveries include a) the elucidation of novel glucose-sensitive post-translational mechanisms regulating ChrEBP and FoxO1 and their functional relevance to hepatic steatosis in mouse models of obesity and type 2 diabetes, and b) analysis of the dual role of Grb14 in insulin signaling and de novo fatty acid synthesis (via the transcription factor SREBP-1c). Moreover, the team has also made methodological breakthroughs through further development of BRET-based assays for the study of therapeutic targets and the screening of small molecules insulin signalling.

This is a very solid, highly focused team with a clear leadership, and with good capacity to attract junior scientists with great research potential. During the last 6 years (2007-12) they have published a substantial number of articles (48), and what is more important a high number of articles of high impact as senior authors (3 original articles and 2 reviews above IF 10: Journal of Clinical Investigation or Cell Metabolism) and 2 original articles in between IF 7-10).

Assessment of the team's academic reputation and appeal

The academic reputation of the team is high as measured by the participation in high impact factor publications as collaborators (1 article above IF 10 and 1 in between IF 7-10). They participated in 18 international Meetings (Keystone symposia ; FASEB conferences, American Diabetes Association) and 12 national Symposia, including 2 plenary sessions at SFD (French Soc Diabetes) and SFE (French Soc Endocrinology) and have organized both local and European (European Association for the Study of Liver, EASL) Symposia. The team is involved in 5 ANR networks and is a Partner of the European consortium FLORINASH FP7 (Gut microbiota and hepatic steatosis). The team leader has also recently become Consulting Editor of the Journal of Clinical Investigation – (Impact factor=13, ranked 4 in Medicine, Research and Experimental category, Q1).

Finally, during the 2007-12 period they have managed to recruit two young scientists as CR1 or MCU at Paris Descartes with great training.

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

The team is clearly highly interactive with the social, economic and cultural environment. This is evidenced by industrial contracts with Sanofi Aventis (2007, 2008, 2011) and Servier (2012) and involvement in annual lectures in High schools. Literature produced for the public/media/government policy is limited but include Science & Vie : « Obésité : 5 nouvelles armes » /obesity : 5 new weapons (S. Guilmeau 2009).

Assessment of the team's organisation and life

Clear leadership and well-organized team.

Assessment of the team's involvement in training through research

This team appears to have developed a great profile for training and development through research. They have supervised 13 PhD students, 17 Master M2 students, 2 Licence Pro 2, and 1 Engineer. The team's members and an assistant professor in particular, are also actively engaged in delivering lectures [generic and specialist (70h/yr) and Master M1/M2 levels (about 40h /yr)] and in organizing an annual meeting on the Education for adults Programme at INSERM since 2005.

Assessment of the five-year plan and strategy

The main research objective for the coming five years aims at building on the success and strengths of the previous period. The feasibility of the project seems particularly high given the availability of core facilities, tools, in vivo models and access to good collaborators. The wish to move towards more translational aspects of their investigations is to be commended as is the incorporation of more global molecular strategies (micro-array, ChIP seq, lipidomics and/or metabolomics analysis). This will allow a good balance between both candidate hypothesis-driven and non-candidate approaches in this research program. This is a highly productive team with great potential to succeed at the highest level.

Conclusion

- Strengths and opportunities:

The team has developed a great track record and made some exciting contributions to our knowledge of hepatic glucose metabolism and its dysregulation during hepatosteaosis using a powerful combination of genetically modified in vitro (cellular) and in vivo (murine) models. There is now greater impetus to continue to demonstrate the involvement of similar mechanisms in human metabolism and pathophysiology. Furthermore, the program is strengthened by incorporation of more translational elements.

- Weaknesses and threats:

The research strategy does not have too many weaknesses. Indeed, the researchers rightly acknowledge a notable weakness in their past research portfolio, in that they should expand their interests to include both relevance and application to human physiology/physiopathology.

- Recommendations:

This is an excellent team that could even help other teams of the department with their expertise in metabolism.

Team 7 : Control of Pancreatic Endocrine Cell Development

Name of team leader: Mr Raphaël SCHARFMANN

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2 (1.3)	2 (1.3)	2
N2: Permanent EPST or EPIC researchers and similar positions	3	3 (2.3)	3
N3: Other permanent staff (without research duties)	2 (1.8)	2 (1.8)	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	4	4
N6: Other contractual staff (without research duties)	5	5	
TOTAL N1 to N6	16	16	9

Percentage of producers	*100 %*

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

• Detailed assessments

Assessment of scientific quality and outputs

This team has produced landmark changes in the field, including the creation of the first human beta cell line. They have identified several modulators of pancreas development and beta cell differentiation that have a potential to be employed in efforts to derive beta cells from ESC, including studies that reveal a potential role of HDACs and their inhibitors in beta cell differentiation. In particular two major scientific achievements are to be highligted here: i) the development of an experimental setup to study human pancreas development, and ii) the establishment of a stable human insulin-producing beta-cell line. These are two major contributions very appreciated by the international community.

During the previous 6-year period (2007-12), this team has produced 61 papers (experimental + reviews) in well-known peer-reviewed international journals, such as Diabetes, Journal of Clinical Investigation or FASEB Journal. Half of this production (32 papers) report on work where the senior author was one of these leaders.

Assessment of the team's academic reputation and appeal

As reflected by the scientific production, this team is undoubtedly one of the best groups working on experimental diabetes in France, with strong international visibility. The team leader is a major player in the field of pancreas development based on several seminal contributions throughout his career, including (among others) work in human pancreas development, identification of regulating signals that have been exploited to make beta-cell like cells from ESC, and now the human beta cell lines. The beta cell line has been requested by the majority of beta cell researchers world-wide. Reputation of the lab is also reflected by the number and quality of the international and national collaborations leading to publications in high-profile journals, and by the excellent level of funding, from both national and international agencies.

Team members participate in numerous advisory committees and are often invited speakers at international meetings. Three members of the team were recently recipients of important awards (2 French awards and 1 European award).

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

Some team members have initiated a start-up that appears to be very successful after six years. They have numerous interactions with industry, including their participation in an IMI (Innovative Medicines Initiative) project. They have filed multiple patents during this period. Dissemination activities in the community have included a seminar in the French Senate.

Assessment of the team's organisation and life

This is consistent with the goals and composition of the team.

Assessment of the team's involvement in training through research

A total of 4 M1, 6 M2, 9 PhD students and 14 post-docs were tutored in the team. This is within the normal range of a research group.

Assessment of the five-year plan and strategy

The group is developing approaches to discover new signals that drive beta cell differentiation, and will target molecules to beta cells in vivo. They will also study the plasticity of the human developing pancreas, attempt to transdifferentiate alpha cells to beta cells, and are searching for new markers to image human beta cells. Other studies will assess beta cell regulators using their cell lines and generate second generation lines. Perhaps most interestingly, they will work with R. Mallone, another team leader of the department, to dissect the regenerative potential of human beta cells during beta cell destruction. Finally, they will investigate the role of Dyrk1a on beta cells and thyroid using mouse models. There is no doubt that the team will continue producing excellent scientific research. Overall, this is a very ambitious proposal, but perfectly doable given the high productivity track record of the investigators.

Conclusion

- Strengths and opportunities:

The group has developed innovative bioassays to study pancreatic development in rodent. In particular, the most important success has been the production of a functional insulin-producing human cell line. This will facilitate the development of new assays to translate data from rodent to human pancreas development and to better understand specific forms of diabetes in human. The collaborative work with pharmaceutical companies has been a strength of the team. Added value for the lab is the creation of a start-up biotech.

- Weaknesses and threats:

The team is now part of the Cochin Institute, yet a well-defined long-term plan involving innovative interactions with the groups of immunologists is clearly lacking in the 5-year plan.

Another potential problem may appear in the near future if too much effort is put on continuing, or further promoting, some ongoing interactions with industry (Sanofi, Astra Zeneca, Bohringer-Ingelheim, Roche, Novo-Nordisk). In general, these trans-national consortia heavily involving the industry are not very productive, and are not characterized by sparkling creativity.

- Recommendations:

The arrival of this team at Cochin Institute should be the opportunity to increase interactions with immunologists and T1D diabetologists, which could eventually lead to the development of knowledge useful to devising innovative therapies to treat inflammation and diabetes.

Team 8 : Iron, Oxygen and Energy Sensing in Pathophysiology

Name of team leader: Ms Sophie VAULONT and Mr Benoit VIOLLET

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	4 (3.2)	3	3
N2: Permanent EPST or EPIC researchers and similar positions	2	2	2
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.)	4	3	3
N6: Other contractual staff (without research duties)	2	1	
TOTAL N1 to N6	14	11	8

Percentage of producers	*100 %*

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

• Detailed assessments

Assessment of scientific quality and outputs

The main research focus of this team is the molecular mechanisms controlling energy, oxygen or iron homeostasis and their dysregulation in common human diseases. The group is at the forefront of research in the field of iron metabolism and homeostasis and is continuing to make seminal contributions to this field and more recently, in the related fields of oxygen and energy homeostasis. Notable discoveries from the group include the demonstration that HIF-2alpha, but not HIF-1alpha, promotes iron absorption in mice. (J Clin Invest 2009) and Metformin inhibits hepatic gluconeogenesis in mice independently of the LKB1/AMPK pathway via a decrease in hepatic energy state. (J Clin Invest, 2011). These are, however, two unrelated research subjects that are being developed in the team.

In the last five years they have published 90+ original articles (& 13 reviews and 5 book chapters, 17 educational publications). 40 publications had at least one member of the team as first and/or last author. Amongst these are several publications in high-ranking journals commanding impact factors greater than 10. Indeed 2 publications in Journal of Clinical Investigation, Impact factor=13, ranked 4 in Medicine, Research and Experimental category, Q1). For some publications, it would have been desirable that the authors had tried to aim for higher impact factor journals. Still, the rather unique profile of research places this team amongst the leading laboratories in this particular field.

While the internally-driven projects have led to some key publications in the field, one wonders why the team does not have the potential for much more than that given their leading position in the field or their unique animal models.

Assessment of the team's academic reputation and appeal

Due to the uniqueness of some of their fields of action and their animal models (AMPK alpha1/alpha2 conditional knock-out mice), the team is very well known within the iron and energy metabolism fields. The team is actively involved with up to 13 international collaborations and is part of the labex GR-EX (Globule Rouge LabEX) comprising an integrated group of 18 internationally recognized scientific teams investigating the major health problems of anemia, red blood cell as well as iron disorders. They have very good visibility.

The scientific interaction network of the team is impressive and includes some of the world leading teams in many different fields, including metabolic homeostasis and cancer.

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

More remarkably, they have also teamed with some non-academic partners, mostly for exploitation of their animal or cell models for pharma purposes. They have filed 2 patents and hold a few license agreements with Amgen and Rigel Pharmaceuticals, San Francisco. Two Industrial contracts involve pharmaceutical companies, the characterization of new AMPK activators and the characterization of new AMPK activators. They also participate to local school programs including operation « apprentis chercheurs » and to associations of patients.

Assessment of the team's organisation and life

The team is organized in a coherent manner according to the research program developed.

Assessment of the team's involvement in training through research

The team only accommodates three PhD students. Given the size of the team, funding and expected projects, it would be more than welcome to find additional space for the formation of master and PhD students.

Assessment of the five-year plan and strategy

The future research plans aim at extending their findings on the cellular functions of AMPK, HIF and hepcidin in the control of energy and iron metabolisms by investigating their involvement in inflammatory response and cancer. The size of the team may be reduced should the ERC funded young investigator become independent. It is not clear how this would impact on a significant part of the HIF-related work currently representing approx. 20% or the research program. Given the highly collaborative nature of this group and their expertise in 'iron phenotyping' and access to some powerful murine models, their plan is feasible and will produce novel and original insights. The project proposition is however too extensive considering the expected size and funding of the lab. Some degree of project prioritization should be proposed. Similarly, the authors barely mention whether the proposed projects will be done fully in their labs or in collaboration with external teams.

Another major caveat for the development of the project is the lack of synergy between the two PIs. In fact two independent and non cohesive projects can be easily identified. Further efforts to create a single team would be welcomed. One would wish that AMPK had been introduced in the research specified in project 3. Despite these observations, there is still a large number of projects that clearly lie exclusively within one of the two big branches of the team.

Conclusion

- Strengths and opportunities:

Both independent projects are scientifically very sound and of high quality. Both PIs are well known in their subjects. The publications are very good and very much cited.

- Weaknesses and threats:

Lack of synergy and consistency between the two proposed projects and PIs.

Further focus on own projects and reduce collaborations. A general feeling of the committee is that some projects are exclusively developed to generate new tools or models for collaboration. This was even presented as an aim.

- Recommendations:

In general, the team should make additional efforts to unify the different experimental branches and optimize their efforts. Alternatively, the AMPK project could join another team more focused on energy metabolism.

The team should concentrate on their own projects, rather than collaborations to further increase the quality of the publications.

The ERC granted scientist should become an independent team leader.

Team 9 : Oxidative stress, cell proliferation and inflammation

Name of team leader: Mr Frédéric BATTEUX

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	6 (2.8)	6 (2.5)	6
N2: Permanent EPST or EPIC researchers and similar positions	4 (2.5)	4 (2.5)	4
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.)			
N6: Other contractual staff(without research duties)			
TOTAL N1 to N6	16	16	10

Percentage of producers	*100 %*

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	5	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	6	6

• Detailed assessments

Assessment of scientific quality and outputs

This team is scheduled to join the Institute in 2014.

The scientific interest and reputation of the team has been built through the investigation of the relevance of Reactive Oxygen Species (ROS) in pathophysiological processes as varied as neoplastic disorders, gynecological diseases, systemic autoimmune diseases and inflammation of infectious origin. The team has contributed to this field with original, interesting and relevant observations. Most of the work performed is clearly translational in nature, having as a long term aim the benefit of patients suffering from the aforementioned diseases. This has generated 68 publications in scientific journals of medium-high impact, 44 of which with main authorship. The wide variety of interests is reflected by the different specialty Journals involved (Pathology, Cancer, Reproduction, Rheumatology, Dermatology, Immunology, Virology). Previous work in the same field provided the basis for 5 patents.

Assessment of the team's academic reputation and appeal

The Team participates to one FP7 EU project named RECAT. FP7 EU grants are notoriously difficult (and laborious) to obtain and this should be taken as a token of excellence.

The unit is affiliated to the DHU (Département Hospitalo-Universitaire) program: "Risk and pregnancy". This is proof that the unit is integrated in a program aiming at coordinating research efforts to perinatal care.

The team participates in the SIRIC/HEGP/Cochin program which is one of the six selected by the French National Cancer institute on the basis of their ability to collect and manage a critical mass of scientific and medical expertise, and technologies around integrated research programs ambitious and coherent.

The team appears to be well integrated in the French network of efforts aiming at improving the synergies between research centers of various institutions and within the Cochin Institute. Members of the team have personal collaborations with several French scientists. They have also some collaboration abroad.

Similarly, Team members have been invited as speakers to international conferences (6 invitations to international conferences), have participated or are participating to clinical trials (three) and advisory committees.

Among the most relevant achievements of the previous term is the establishment of a new mouse model of systemic sclerosis that recapitulates the three major features of the disease, namely fibrosis, vasculopathy and auto-immunity. In this respect it should be stressed that none of the existing mouse models of systemic sclerosis fully recapitulates in its entirety the human clinical disease.

As a general statement, the team has been deeply involved in activities that increase its academic reputation.

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

All team members have activities that impinge on the economical and cultural environment. The 5 patents represent the best attraction for activating economic network in the field of therapeutical or diagnostics. Moreover, their involvement in founding in year 2000 a start-up company which is still alive, their collaborations with pharma companies (two) and their major role in public awareness of sexually transmitted infections should be stressed.

The social impact is shown by the participation of the team leader in the scientific committee of the Martin MIDY Foundation and by the involvement of team members in public health.

Assessment of the team's organization and life

The close link between biologists and chemists is the core of the Unit which allows the development of new redox modulators for different target diseases. The other two major characteristics are 1) the interdisciplinarity of the investigators (immunology, oncology, dermatology, virology and gastroenterology) and 2) and the close interactivity with various clinicians (gynecology, oncology , dermatology).

Assessment of the team's involvement in training through research

31 students and 19 MSc have been trained in the unit. 9 students have undertaken their PhD studies and 4 of them defended their PhD thesis. All permanent members are involved in teaching medical students and some of them also students in sciences. program the team has been involved in exchanges and training with other European partners thgrough a participation to the FP7 "People".

Assessment of the five-year plan and strategy

The team proposes a number of different subprojects articulated along the common theme represented by ROS and the specific themes for which each member has more interest or share interests with other team members. Thus variety rather in depth investigation characterizes the project. This most probably reflects the fact that team members are clinicians.

ROS and ovarian cancers (OC). This project is based on the assumption that resistance of OC to chemotherapeutic agents is directly linked to alteration of RedOx states and that these alterations influence cancer cells via signaling through ERK and TOR pathways. Thus, the authors propose to assess the in vivo effect of altering ERK and TOR signaling to tumor growth when cancer cells are injected in nude mice. (The limitation here is that chemical inhibitors of ERK and TOR will impact on mouse adaptation to tumor, for instance by influencing angiogenesis, independently of the effect of these drugs to cancer cells). Furthermore they propose to establish a metabolomic analysis of the cancer cell lines.

In addition, they want to assess ROS production and antioxidant enzymes levels in various tumors directly generated from patients. Evidence has been generated by others (Curie Institute, Paris) with whom they plan to collaborate, that overexpression of miR-200a and miR-141 in ovarian cancers mimics p38 deficiency and "correlates" with oxidative stress signature. However, response to chemotherapy requires also an intact RedOx status. Thus, they aim at assessing the relationship between biological cancer markers and response to treatment.

The other side of the coin is the possibility of counteracting chemotherapeutic agent peripheral nerve toxicity by modulating ROS production, which they want to assess. Thus, they have generated preliminary data (not presented in detail nor in the report nor during the oral presentation, that magafodipir specifically reverses potassium channel toxicity induced by oxiliplatin.

ROS and inflammatory genital tract disorders. The rationale is here given by original observation that normalization of ROS production impacts on endometriotic cell proliferation. The original hypothesis to be tested is that Foxl2 and its regulator Dlx5 are deeply involved in two key phenomena, ROS generation and sexual hormones production by endometrial cells. The plans are to carry on this part of the project in collaboration with a CNRS team. This part of the project appears to be very promising and of major interest. At the moment it remains highly speculative.

They also want to investigate etiologic factors responsible for endometriosis, in particular the hypothesis that autoantibodies directed against endometrial cells may play a role. Here they stress the point that endometrial cells from endometriosis are in many ways different from normal endometrial cells, thus they propose to study serum reactivity against cells from endometriosis rather than cells form normal endometrium, and this by 1D and 2D western blots. Here the weak point is that the presence of autoantibodies does not indicate per se that they are responsible for the phenomenon. Additional information on altered glycosylation of proteins on endometrial cells may impact on natural immune cells possibly involved in the clearance of ectopic endometrial cells has been provided during the oral presentation.

A very speculative approach on the role of Vanin-1 and its importance in the metabolism of pantethine and pantonthenic acid is was provided during the oral presentation.

CXCL4 – ADAM expression in endometrial tissues. Not enough details were given to understand whether this is a histopathological study or whether functional assays will also be performed.

ROS, infections, inflammation genital tract. Maternal *T. pallidum* infection results in congenital newborn infection or in fetal death, stillbirth or death shortly after delivery. The aim of the project is to identify molecular targets involved in transplacental passage of *T. pallidum* and the consequent inflammation possibly responsible for the loss of maternofetal tolerance. The authors aim at establishing a mouse model of *T. pallidum* infection to dissect innate /adaptive responses. No details are given on previous experience with this mouse model and how relevant this is to the human situation. Then, they plan to assess pro-inflammatory cytokines and ROS generated during the immune response on cyto- and syncytio-trophoblasts in vitro and study signaling pathways. No details are given on the methods envisaged.

ROS and skin. –I- Skin cancer. Merkel cell carcinoma (MCC) cell lines have been established with differences in virus integration, possibly reflecting in vivo situations. The authors aim at investigating the role of ROS in the proliferative characteristics of these cell lines. Furthermore, the role of distinct viral proteins will be assessed by transfection in human fibroblasts aiming at identifying mechanisms leading to immortalization and their link to ROS metabolism. One member (AP-HP fellowship) appears to be a key person for the success of this project keeping contacts with external collaborators (APOBEC3 enzymes).

ROS and skin. –II- Skin inflammation. This relates to the new original mouse models of SSc that has been developed and characterized by team members. Recent findings point to the possibility that in their model microparticles generated from endothelial cells under stress could be mechanistically involved in fibrosis development. Thus, it is logical to investigate their role and the proposed approach (KO mice for proteins putatively important in microparticle formation obtained by collaborating authors) is clearly the right strategy to pursue the aim.

Through a collaboration with a team at UTSW, Dallas, TX, USA, the authors have identified an overexpression of polo-like/Aurora/CDC25 pathway in fibroblasts from HOCl-exposed mice. They aim at investigating the role of this pathway in murine and SSc human fibroblasts by using unspecified inhibitors. This is presented as a fishing expedition aiming at finding novel pathways of possible relevance to the human situation.

ROS and skin. –III- Skin inflammation of infectious origin. The authors have identified a relationship between ROS production and IL-8 production by keratinocytes in one hand and *P. acnes* growth in the other. They plan to study *P. acnes* strains obtained from clinical samples of various types of acne to investigate whether various *P. acnes* strains have differential capabilities to induce keratinocyte responses. This is logical (the proposed method is the multilocus sequence typing (MLST). No discussion was provided to allow understanding the power of this methodology).

The authors have preliminary data indicating that *S. pyogenes* results in keratinocyte death via excessive production of ROS. Furthermore, several pro-inflammatory cytokines are produced. *S. pyogenes* activity is reduced by blocking the integrin beta1. Thus the authors want to further assess the molecular cascade of events linking *S. pyogenes* to keratinocyte responses particularly focusing on Syk, known to be implicated in integrin signaling. The project here appears to be feasible, though not many details were given.

Conclusion

- Strengths and opportunities*:*

A major strength is represented by the experience of the team members proved by previous abundant original work published in medium-high impact scientific journals. Team leaders and their coordinator have proved without doubt their excellence in their domain of expertise. An additional strength is the common focus on ROS across a variety of medico-scientific topics belonging to different fields of medicine. Thus, already present as well as continuously developing expertise on ROS will certainly favor the productivity and impact on quality of the team members and their collaborators. The authors have already established a number of collaborations with other scientists that will certainly provide tools or material allowing the correct development of the proposed research. Most of the specific projects that the authors propose to develop are designed in a way that results could be published whether or not supporting the hypothesis that has driven the specific project.

- Weaknesses and threats:

The strength of the team, which is experience with ROS, is at the same time a weakness, because team members tend to use the same paradigm across different models and disease situations in a transversal manner. This may reduce the in depth enquiry to which specific phenomena are submitted.

- Recommendations:

The committee believes in the potential of the team and the strength of a medically-oriented approach, which is a specific characteristic of the team members. It will be important to profit from the novel affiliation of the team with the Cochin Institute to get more interactions with other scientists of the Institute aiming at formulating mechanistic questions. This should favor experimental approaches to better investigate mechanisms underlying the pathophysiological processes in which they are interested. Therefore, it is highly recommended to facilitate the incorporation of basic scientists in the team and the location of the laboratory close to other teams with a rich experience of basic science.

Team 10 : Stem cell environment and skeletal muscle homeostasis

Name of team leader: Ms Bénédicte CHAZAUD

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2 (1.5)	2	2
N2: Permanent EPST or EPIC researchers and similar positions	1	1	1
N3: Other permanent staff (without research duties)	1	1	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)			
N6: Other contractual staff(without research duties)	1	1	
TOTAL N1 to N6	5	5	3
Percentage of producers		100 %	

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

• Detailed assessments

Assessment of scientific quality and outputs

Team 10 is producing an outstanding research on the molecular mechanisms that control the interactions between muscle stem cells and their environment. They recently expanded this work to include the examination of these interactions in human myoblasts and during myopathies (collaboration with team 11).

The initial work in the examination period, showed that satellite cells were often located near capillaries, and that endothelial cells stimulate myoblast growth, while myogenic cells have a pro-angiogenic effect on endothelium (ACL-2007-2). This work then led to the discovery of the role of ang1/Tie-2/ERK1/2 signalling in satellite cell function. This resulted in a publication in the prestigious Cell Stem Cell (ACL-2009-1), which has now been cited a creditable 41 times. This can be considered highly original work, establishing that there are reciprocal interactions and signaling between resident muscle stem cells and endothelium.

The other main contribution by team 10 during the review period is the pioneering work on the trophic roles of macrophages and inflammation on the regulation of muscle stem cell function. Initially they showed that inflammatory monocytes recruited after muscle damage change into anti-inflammatory macrophages later in the regenerative process to support myogenic differentiation. This resulted in another prestigious publication in J Exp Med (ACL-2007-1). More recently, the team has found that only one wave of monocytes/macrophages enters injured muscle, but then modifies its phenotype from a pro- to an anti-inflammatory phenotype. Investigation of the molecular mechanisms showed that AMPK is essential for the acquisition of the anti-inflammatory phenotype by intramuscular macrophages at the time of inflammation resolution.

Importantly, these observations have also been repeated in man, to show that both in human and mouse, muscle repair is first associated with pro-inflammatory, then anti-inflammatory macrophages. Importantly, the factors that mediate this signaling between macrophages and muscle stem cells in man have been identified and include IL6, IL1bâ, VEGF, TNFaá and TGFbâ (Stem Cells). Thus these mouse-based investigations are providing the solid foundations for work directly in man.

Finally there is some interesting data on how combined transplantation of macrophages with myogenic cells improves the survival, expansion and migration within muscle tissue of the later population (PLoS ONE).

Together this body of work adds significantly to the understanding of how muscle regeneration is controlled by cells other than stem cells. Importantly, this work in mouse is being confirmed in man where possible, and projects involving cells from myopathic patients are also highlighted. This is a welcome development.

Assessment of the team's academic reputation and appeal

The reputation of this young and recently independent team is growing rapidly, and they are already held in high esteem within the myogenesis community. The PI already has a highly-respectable Thomson-Reuters H-index of 17. The team is well-embedded in the French myogenic community, and these are productive interactions as shown by their many collaborative publications. There is also an extensive international collaborative network, with several long-term visits from invited researchers (from Hungary or from Denmark) allowing access to tools, reagents and expertise.

Such extensive collaborations are a testament to their quality. Furthermore, their ability to attract funding is evident. The team is also a member of the EU FP7 network Endostem (activation of vasculature associated stem cells and muscle stem cells for the repair) further demonstrating the high regard this work is held in. The senior members of the group regularly speak at National and International meetings.

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

One of the PIs of the team is participating to several clinical trials either as the main coordinator or as a partner. He is also involved in several patients organizations.

The team is also implicated in knowledge dissemination to a broader audience: publication in Magazine Sport et Vie.

The PIs are involved in the organization of conferences directed either at the muscle community (monthly muscle club with presentations of the latest data in the field) or at a general audience (Journée de l'innovation).

Assessment of the team's organisation and life

The team is composed of about 10 people with three PIs, one more clinically oriented (1 PU-PH) and two basic scientists (1DR2, the team leader and 1 CR2). It appears that there is a good synergy between the three PIs, each being involved in the different projects according to his/her expertise. Due to the relatively small size of the team, the organization looks rather simple with a very close collaboration between all members.

The project appears very coherent. Funding has been obtained by the different PIs. The team appears self-sufficient in terms of funding with a variety of grants obtained from different sources (EC FP7, ANR, AFM,…).

Assessment of the team's involvement in training through research

Two theses have been defended in the team in the past 5 years and 4 are currently underway. The two students who completed their PhD are occupying post-doctoral positions. During their PhD, they had a good production in terms of articles.

There are regularly M1 and M2 students in training and all three PIs are involved in teaching and coordinating M1 and M2 degrees as well as some university diplomas more specifically aimed at medical students.

The team also participates in the scientific awakening of high school students (apprentis chercheurs-L'arbre des connaissances).

Assessment of the five-year plan and strategy

The team members have defined themselves by investigating the regulation of muscle regeneration and muscle stem cell function through interactions with the environment. This is an important topic and they are making good progress towards understanding the signaling molecules that communicate this control. Extending this work to investigate also how these regulatory mechanisms operate in man and during disease is a sensible move, especially considering the growing governmental emphasis on translational research and the prevailing funding situation (e.g. support from the AFM).

Therefore their two broad aims (as stated below) are entirely appropriate:

i) identification of the molecular pathways at work in normal muscle regeneration,

ii) exploration of these cell interactions in the context of degenerative muscle diseases.

Conclusion:

- Strengths and opportunities:

- Original “niche” of research topic,

- Strong funding,

- Excellent quality of publication,

- Complementarity between basic and clinical research,

- Young dynamic team,

- Good collaborative network.

- Weaknesses and threats:

- Infrastructure: strong dependence on adequate cell culture facilities and animal facility,

- Dependence on obtention of human samples for some projects,

- Rapid growth of the team.

- Recommendations:

The team has grown very rapidly in the past 5 years and is now fully independent. This is always a critical passage and care should be taken to consolidate their organization, to pursue an outstanding research and therefore to support them where necessary.

Team 11 : Genetics pathophysiology of intellectual disability and neurodevelopmental disorders

Name of team leader: Mr Jamel CHELLY

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3 (1.7)	1 (0.5)	1
N2: Permanent EPST or EPIC researchers and similar positions	7 (5.2)	6 (4.2)	6
N3: Other permanent staff (without research duties)	2	3	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	2	2
N6: Other contractual staff(without research duties)			
TOTAL N1 to N6	13	12	9

Percentage of producers	*100 %*

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	5	
Theses defended	4	
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	4	4

• Detailed assessments

Assessment of scientific quality and outputs

The four following themes were developed with a peculiar emphasis on genes related to the tubulin gene family and genes related to microtubule dynamics (tubulopathies) with respect to their pathophysiologies of neurodevelopment disorders.

A- Genetics of Intellectual disability (ID) and malformation of cortical development (MCD).

The team is a founding member of the European X-linked Mental Retardation Consortium. The research work focussed on the characterization of ~10 genes involved in ID and MCD. From these were identified DCX, TUBA1A, TUBB2B, TUBB3, TUBB5 which harbored mutations correlating with the MCD pathologies (including the group of polymicrogyria). These studies culminated with an important article published in Nature Genetics. The genes were further characterized using an in vivo shRNA approach and in utero electroporation. Complementary collaborative work was also performed showing that the mutated forms of tubulins present defects in heterodimerization properties and microtubules dynamics.

B - Functional studies of ID proteins: OPHN1- and IL1RAPL1-related ID.

The team has studied XLID genes mostly through the use of the OPHN1 and IL1RAPL1 mouse models. The OPHN1 mice reproduce the patient phenotype with abnormalities in behaviour (spatial learning, lateralization and sociability) and dilated cerebral ventricles but no cerebellar hypoplasia. ophn1 regulates the processes of synaptic vesicles endocytosis. ophn1 inhibits a RhoA/ROCK signaling cascade and treatment of ophn1 KO mice by ROCK kinase inhibitors were able to partially restore some behavioral, anatomical and physiological phenotypes observed in the mutant. The IL1RAPL1 mice present signs of hyperactivity and also deficit in the contextual version of the fear-conditioning test. In a collaborative work the team has found that IL1RAPL1 interacts with post-synaptic proteins from the MAGUK protein family comprising PSD-95 and that loss of IL1RAPL1 led to a significant reduction of excitatory synapses together with a reduction of LTP in hippocampus but no alteration of synaptic efficacy.

C – Pathophysiology of Rett syndrome.

Rett syndrome is one of the leading causes of mental retardation and developmental regression in girls. A major gene related to RS is MECP2 (90% of the cases). In differential transcriptomic studies between WT and MECP2-deficient cells STMN2 was found to be down-regulated among 22 others. STMN2 down-regulation was confirmed in MECP2 mice, with impaired microtubules dynamics characterized in MECP2-deficient astrocytes.

D - Non-myogenic cells and their role in muscle regeneration and pathogeny of neuromuscular disorders.

This theme was led by a scientist who is proposed to be an independent team leader in the next mandate (team 10). The work developed here is based on, and a continuation of, an original observation published in 2007 in J. Exp Med. Non myogenic environmental cells are crucial in the regulation of muscle stem cell fate. Removal of circulating monocytes at the time of injury totally prevents muscle regeneration. Analysis of the interactions between different types of macrophages and myogenic stem cells showed that proinflammatory macrophages stimulated the proliferation of muscle cells and inhibited their fusion rate. Conversely, anti-inflammatory macrophages stimulated the entry of muscle cells into the terminal differentiation program and stimulated the formation of large myotubes. Additional studies showed that these cellular processes are regulated by IL6, IL1ß, VGEF, TNFα and TGFß factors secreted by different sub-populations of macrophages. Complementary work led to another original observation showing that autocrine and paracrine angiopoietin 1/Tie-2 signaling promotes muscle satellite cell self-renewal (published in Cell Stem Cell).

Overall the team has published a very impressive 102 ACL articles of which 50 were signed by a member of the team as senior author. These include articles published in Nature Genetics, Human Molecular Genetics, Cell Stem Cell, J Neurosci, Brain, Mol Psychiatry. Members of the team are also collaborators in exdellent publications in Nat Neurossci, Curr Biol and Cell.

Of note, 2 publications from this team (in Nature Genetics and in Cell Stem Cell) are among a total of 15 publications pointed out by the director as the Cochin Institute scientific highlights.

The financing of the team is excellent.

Assessment of the team's academic reputation and appeal

This team has a stellar international reputation. Members are regularly invited to participate in national and international conferences. The leadership and attractiveness of the team is also illustrated by a number of awards, by the inclusion in several collaborative networks at the international and European levels. Of note, the team leader was awarded the INSERM Prix de la Recherche 2010.

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

No formal partnership with economic network is currently in place. However, given their field of investigation in human genetic disorders and mental disabilities, the team is extremely concerned with societal problems and issues. The group was also active in technology transfer, mostly via local collaborations at Cochin and associated hospital.

Assessment of the team's organisation and life

In accordance with the goals of the team.

Assessment of the team's involvement in training through research

The team is implicated in teaching at a high level, by welcoming master and PhD students. The quality of this training is evident from the fact that several former members have now gained a strong reputation as PIs in other institutions.

Assessment of the five-year plan and strategy

The global aim is to further our knowledge of the mechanisms involved in normal brain health and in conditions such as intellectual disability and developmental disorders, and to transpose this knowledge into clinical applications as to improve diagnostic and genetic counseling and identify new therapeutic targets.

This will be achieved in a very pragmatic way by focusing on a few selected group of human genetic disorders such as intellectual disability, brain malformations and Rett syndrome, for which access to clinical material and expertise are guaranteed.

The program is organized into the following well defined workpackages.

1. Identification and investigation of novel genes.

2. Functional consequences of mutations on excitatory synapses.

3. Synaptic activity and circadian rhythm.

4. Pathophysiology of Rett syndrome and evaluation of therapeutic approach.

This organizational chart is highly professional, based on the established strength of principal investigators, with ample opportunity to collaborate in terms of conceptual approaches, technology and transfer.

Conclusion

- Strengths and opportunities:

- Impressive records,

- Outstanding experience in human genetics and neuronal migration,

- Collection of biological resources, clinical and imaging data,

- Ambitious project,

- Excellent funding,

- Link to clinic.

- Weaknesses and threats:

- Paucity of research projects on neuronal biology conducted by the other teams of the Cochin Institute,

- Bio-informatic expertise.

- Recommendations:

There is no doubt that the outstanding quality of the work should be maintained in the future. Their interaction with other Cochin groups should be encouraged and they should find support to improve their expertise in bio-informatcs and large-scale data analysis.

Team 12 : Cell cycle and Liver pathophysiology

Name of team leader: Ms Chantal DESDOUETS

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2	1	1
N2: Permanent EPST or EPIC researchers and similar positions	2	2 (1.8)	2
N3: Other permanent staff (without research duties)	1	1	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1	1
N6: Other contractual staff(without research duties)			
TOTAL N1 to N6	6	5	4

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

• Detailed assessments

Assessment of scientific quality and outputs

This team has focused its activity on the study of essential mechanisms involved in the response to liver injury and regeneration. Two major projects have been pursued: senescence, fibrosis and growth hormone signaling; and the regulation of normal and pathogenesis-associated hepatocyte polyploidization. The scientific output is excellent. During 2007-12 ten publications in high quality international journals were produced in which first or last authors were members of this team. In particular, two articles were published in the Journal of Clinical Investigation. Others were published in good journals such as J Cell Sci (X2) Am J Pathol (X2), Mol Therapy, Endocrinology. ,Numerous contributions to international meetings were also made. These include several oral and poster communications to the most well-recognized scientific congressess in the field of hepatology. For the size and composition (number of students) of the group this is an outstanding prodution. Particularly, the participation of the team in several national grants brings in third party grant money to the group and that causes also a diversification of multiple projects. This strengthens financially the group and helped attract researchers thanks to the available funding.

Assessment of the team's academic reputation and appeal

The leaders of this team are well-recognized scientists in their field of activity. This assertion is supported by: the collaboration with other researchers (french-12 publications- and international-4 publications) as validated by numerous joint publications in high ranking journals, the obtention of substantial funding from public agencies, the invitation of the team's PIs to participate as speakers in international conferences. In particular, the team leader is recognized as an international expert in the field of hepatocyte cell cycle regulation and the control of cell ploidization. Most importantly, the team leader achieves significant citation numbers over time, with an Average Citation of 19, which the evaluators call highly significant for a young group leader.

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

This team has also participated in activities addressed to the general public, including the introduction of high school students in the field of biomedical research. They have also co-organized introductory meetings for young researchers. One of the co-PIs also refers various collaborations/partnerships with the pharmaceutical industry, although these are not described in detail. The team leader mentioned at the side visit that she is involved in university teaching courses of ~10 hours per semester and she coorganizes Cochin workshops.

Assessment of the team's organisation and life

There are two group leaders within this team, but one moves up to the upper management of Institute Cochin and will join team15. Thus,the team leader has reached independence and she will head the group alone for the next phase.

Assessment of the team's involvement in training through research

Three PhD thesis have been defended and these were finished within a short time which is excellent, and 12 master's degree students have worked within this group over the past five years. In the evaluators opinion this is a fair number of students given the size of the team. In the composition of the team for the next five years there are already two PhD students enrolled, together with one M2 student and a "Professional Biology Training" person.

Assessment of the five-year plan and strategy

The five-year plan involves a reorganization of the team. Two prominent members will leave the team, a new junior sicentist will take on more responsibilities under the direction of the team leader. The team will be also reinforced by a young scientist with strong background in inflammatory pathways. This is an emerging team with a young leader that has an excellent background (expertise and publication record). The research project will be logically focused on the pathophysiology of hepatocyte ploidy. There are three major areas of research:

ploidy and metabolic disorders, p38-MAPK and LKB1 signaling in ploidy and DNA integrity maintenance in liver regeneration, and the interface between inflammatory microenvironment and chromosomal integrity. These issues will be analyzed using state of the art genetic mouse models and experimental interventions/technologies. These are very interesting topics for research with clear pathophysiological impact. The project includes a descriptive part in which the emergence of polyploid hepatocytes will be assessed in different experimental models of HCC and NAFLD, as well as in clinical liver samples from patients. In addition, the role of ploidization on specific biologicals aspects of hepatocytes will be analyzed. To this end the researchers have recently developed a method to isolate different hepatocyte populations with different ploidy from the liver of control and mice with NAFLD. This will allow to examine the influence of ploidy on hepatocyte metabolism, proliferation and their capacity of liver repopulation in transplantation experiments.

The project could be further strengthened by taking into account the three following points.

1) A number of disease models have been mentioned (e.g. DEN injection, but a chemical carcinogen causes many genetic alterations that can hardly be controlled. DEN settles strain specific mutations in the first 48 hours after injection). The use of genetic HCC models with defined progressive stages might be more powerful to study the proposed control of ploidy processes. For instance, they could make use of an inducible Cre action to promote HCC. They could question cancer development in light of metabolic questions as they have done successfully before associate with polyploidy. This might require a timed analysis of larger cohorts of animals on a genetic model that progresses with or without inflammation towards HCC. The Institute Cochin has very strong groups working on metabolism and to team up here could be a benefit.

2) The team should consider to work with immortal primary hepatocyte cell lines devoid of $p19^{ARF}$ cell cycle inhibitor proteins since that allows the establishement of true hepatocyte cell lines (Mikula et al., Hepatology, 2004 Mar;39(3):628-34), where e.g. certain key genes could be floxed and then deleted in vitro by transient Cre expression (or Cre-eGFP fusion protein to allow for sorting). Then passage numbers and genetic characterization would be facilitated to be analyzed. The use of a cell line model should be considered as a secondary alternative. Similarly, the culture media and the cell line working models could be profiled for the metabolome. In light of limited mouse space immortal hepatocyte cell lines might be a benefit.

3) The generation of liver cell chromosomal abnormalities could have been linked with comparative genomic hybridization (CGH) analysis to control for deletions and gains in light of copy number variations.

Conclusion

- Strengths and opportunities:

The expertise of the scientists involved as well as their proven capacity to conduct high quality research, guarantee the achievement of their objectives.

The team is very well focused and coordinated.

The external and internal collaborations are excellent, and further support the viability of the studies.

The team is well funded.

- Weaknesses and threats:

A more translational orientation is observed in the proposed project for the next five years, compared with the previous period. Collaborations with leaders in the field of human liver disease are underway. However, this is still a point to be reinforced.

One further weaknesses could result from limitations in transgenic mouse housing.

- Recommendations:

Increase the interaction with industrial partners.

In the research plan, it would be interesting to consider possible dietary/pharmacological interventions to modulate the alteration in hepatocyte ploidity involved in liver disease progression. This might increase the interaction with industry and the generation of patent applications. In addition, given the role of oxidative stress in pathological poliploydization demonstrated by this team, they would be in a very good position to collaborate with Team E9 in Cochin, who has developed new oxidative stress modulating molecules.

The experimental models proposed for some parts of the future project could be complemented as detailed above in three bullet points.

The Institute Cochin should ensure to provide enough transgenic mouse space (300 cages are a minimum).

Team 13 : Genetics, development and physiopathology of skeletal muscle

Name of team leader: Mr Pascal MAIRE and Ms Athanassia SOTIROPOULOS

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2 (1.2)	2	2
N2: Permanent EPST or EPIC researchers and similar positions	6 (5.5)	5 (4.5)	5
N3: Other permanent staff (without research duties)	3	3	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1	1
N6: Other contractual staff(without research duties)	2		
TOTAL N1 to N6	14	11	8

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	5	
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	7	6

• Detailed assessments

Assessment of scientific quality and outputs

This team has worked on the role of Six/Eya genes for many years, latterly with an emphasis on their role in developmental myogenesis. The team continues to explore Six/Eya function. The interactions with BMP and canonical Wnt/sonic hedgehog signaling is particularly exciting, as it is a step towards unifying interacting pathways for myogenesis.

Recently, their remit has expanded towards also examining the role of Six/Eya genes in skeletal muscle growth, and their function in repair in adult, with a recent 'Journal of Cell Biology' publication on Six1 and adult muscle stem cells [arguably it might have gone to a higher-impact journal, but for a prior publication from the Takeda group (Yajima et al (2010) Exp Cell Res. 2010 Oct 15;316(17):2932-44].

The work of the co-team leader has added a further dimension to the team, with her work on the role of SRF in muscle aging, hypertrophy and atrophy. This is particularly interesting, and resulted in a 'Cell Metabolism' paper in 2012. More recent work has shown that SRF is required for hypertrophy and also dissected downstream signaling involving interleukin expression, identifying a new role for Srf in translation of mechanical cues into paracrine signals.

Such work on adult muscle has direct implications for muscle disease and sarcopenia, as recognized by the team, and is a sensible re-orientation.

Their output is good with many publications including PNAS and Cell Metabolism, with many others in respectable middle-ranking journals (e.g. Dev Biol).

Assessment of the team's academic reputation and appeal

The team is held in high esteem within the myogenesis community, with a reputation for solid and careful science. The team is well-embedded in the French myogenic community, and these are productive interactions as shown by their many collaborative publications. There is also an extensive international collaborative network, allowing access to tools, reagents and expertise. Such extensive collaborations are a testament to their quality. It is possibly surprising however, considering the size of the group and its many publications, that there are not more 'invited speaker' accreditations for the more senior members of the group.

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

In general, this aspect of the team is not well developed. It is arguable that the recent shift in focus towards examining more adult muscle function and repair, with their direct implications for muscle disease and sarcopenia, will have a larger social economical benefit than research restricted to developmental myogenesis. Much of the work is on mouse as it is such a powerful tool, but it would be useful to have a clearer idea of the extent that these results pertain to man. Similarly, although comparatively rare, rhabdomyosarcoma is worth investigating, especially as the sarcoma primarily affects children/adolescents. There is a patent of potential economic impact.

It would have been useful to see some speculation in this section on how the solid academic findings, for example on SRF in adult muscle function, could be harnessed for social economic benefit.

Assessment of the team's organisation and life

The team currently comprises 16 members, with two due to retire in 2014. There seems to be an appropriate balance at present between experienced career scientists (CR1/CR2), students and support staff. The addition of a new scientist to the team has brought in expertise on adult muscle stem cell function, as well as an extension of the core work of the team into SRF signaling and muscle function in adult. These additions seem well integrated into the research strategy.

Assessment of the team's involvement in training through research

Research-based training – as stated there have been 5 PhD theses completed in the lab since 2007, with 3 PhD theses currently in progress. Furthermore 4 BTS students, 6 licence pro students, 9 Master students, 1 Pharmacist Doctorate, and 4PhD students have also been trained by the team. Thus, this seems a highly productive and effective research-training environment.

Assessment of the five-year plan and strategy

The team proposes to continue investigating signaling in developmental and regenerative myogenesis in parallel, focused around Six/Eya and Srf. The team has produced several important gmo mouse models over recent years that have proved very useful in dissecting the role of Six/Eya genes, and new tools continue to be generated, for example an inducible KO of LRRFIP2, as well as a gain of function inducible LRRFIP2 transgenic line.

The continuing move towards investigating adult muscle function seems sensible considering the prevailing funding situation, and the large amount of support awarded by the AFM. Similarly, undertaking projects that can tap into funding for cancer also seems a rational strategic move, although Gli/Shh signaling in rhabdomyosarcoma appears somewhat removed from the core work of the team.

As documented, there is a collaborative project on cardiac muscle remodeling. This work falls outside the main focus of the lab, and it seems sensible to not continue it, as already indicated by the team.

Conclusion

- Strengths and opportunities:

- strong basic research,

- good funding,

- excellent project.

- Weaknesses and threats:

- limited link with clinics,

- limitations in transgenic mouse housing.

- Recommendations:

There is no doubt that this team should pursue their excellent work in the future. Their findings, mostly obtained from mouse models, could be the basis of more translational approches in human.

The Institute Cochin should ensure to provide enough transgenic mouse space.

Team 14 : Study of normal and pathological hematopoiesis

Name of team leader: Mr Patrick MAYEUX and Mr Didier BOUSCARY

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	5 (2.75)	5 (3.5)	4 (3)
N2: Permanent EPST or EPIC researchers and similar positions	6 (4)	7 (5)	7
N3: Other permanent staff (without research duties)	2	2	
N4: Other professors (PREM, ECC, etc.)	1 (0.5)	1 (0.5)	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	2	2
N6: Other contractual staff(without research duties)			
TOTAL N1 to N6	15	17	13

Percentage of producers	*100 %*

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	7	
Theses defended	7	
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	9

• Detailed assessments

Assessment of scientific quality and outputs

The team has produced interesting results in several fields in normal and malignant hematology. One of the main contributions is about normal erythropoiesis: team leaders and members have good records in the field. During the last labeling period, they described several regulatory mechanisms of EpoR, notably the association of TfR2 with EpoR complex. This expertise in physiological hematopoiesis has been successfully translated to myelodysplastic syndromes. Several original mechanisms of dyserythropoiesis in MDS have been discovered. These works have been published in top hematology journals (Blood, Leukemia etc..).

The other main topic investigated is the deregulation of PI3K/AKT/mTORC1 in AML. The goal was to uncover the mechanism responsible for constitutive PI3K activation in blast cells and the lack of efficacy of rapamycine in this disease. The most original result obtained was the demonstration that blast cells require high level of protein synthesis for survival, opening interesting development about AML cell metabolism. Results from this axis have also been published in major hematology journal.

Besides these main topics, the team has been involved in several collaborative studies with national clinical study groups like Groupe Francophone des Myélodysplasies and GOELAM, and other teams focused on erythropoiesis and genomic. These collaborations have led to significant papers.

Overall, the work performed in the team is of good quality with a number of important findings in the last few years mostly around the erythropoiein receptor and the myelodysplastic syndroms. Publications are predominantly appearing in Blood or Leukemia, journals leaders in the field of hematology and both with an impact factor around 10. Since 2007, 56 original articles and 18 reviews have been published by the team.

As indicated by the co-direction between a full-time researcher and a hematologist of the Cochin Hospital (a feature that will be maintained in the future), this team has succeeded in maintaing a good balance between fundamental and clinical research with both aspects of equal quality.

Assessment of the team's academic reputation and appeal

The team participates to a Labex, and one of the team leader is the Head of a work package in this Labex. The team expertise in myelodysplastic syndroms and acute myloid leukemia is acknowledged by the tights links existing between the unit and the groupe francophone des myelodysplasies and the group GOELAMS (Groupe ouest-est des leucémies aiguës et maladies du sang). The team has also regularly been labellised by the Ligue Nationale contre le Cancer.

Overall, the team is well known, nationally at least, in the hemato field for their work on AML and mTOR pathway and in erytropoesis.

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

One international patent in 2009. Three contracts with pharmaceutical companies during the 2007-2012 period.

One of the groups is partner in an ANR RPIB (Recherches Partenariales and Innovation Biomédicale) obtained in 2011.

The integration of a number of clinical-scientists and the formation years ago of the GOELAM banking is certainly a plus for this team.

Assessment of the team's organisation and life

The team organization appears to be based on an equal contribution of basic researchers and clinicians in the scientific themes and objectives. The strong involvement of clinicians allows for an important access to samples from patients with myelodysplastic syndroms.

Publications indicate that the team members work closely together as many are co-signed by several PIs.

The team leader is also reponsible for one of the core facilities of the Cochin Institute, the proteomic platform which is the facility that is the most used by outside laboratories.

The merger with an incoming group is completely logical based on research thematics and will reinforce the fundamental research aspect of the team, also opening new projects lines.

Assessment of the team's involvement in training through research

A good number of PhD students have been trained by the unit over the years (7 PhD have obtained their thesis) 7 new PhD have now join the team. A number of PIs have teaching involvement (master, PhD courses).

Assessment of the five-year plan and strategy

The project is coherent and builds on previous work performed by the team aiming to characterize further the mechanisms of erythropoiesis and signaling in leukemic cells. The program on MDS except on dis-erythropoiesis has not been presented which is a strong translational part of the team in the past.

In each of the two main thematics, new items are being proposed such as the study about the cytokines GDF15 and GAS6 produced during erythroid differentiation in theme 1 and the opening of the signaling studies to normal hematopoietic precursors and not only AML cells in theme 2.

Considering the expertise present in the team, feasibility appears high. The projects appears safe without any high risks directions.

However, the lack of in vivo model as well as ex vivo long-term culture of patients samples make the project less competitive now. The team mentions that collaboration has been engaged with other groups to remedy to this. Nevertheless, no information has been given on this collaboration during the presentation questioning their position on the development of this type of model. Using leukemia cell lines and in vitro short term assay on patient samples seems a limited factor for some experiments: like transduction of leukemic cells to look at functionallity of Pum.1 and 2 or PIM1 and 2.

Conclusion

- Strengths and opportunities:

The strength is certainly on the quality and the number of the full time researchers and hematologists. The close link between scientists and clinicians and the capacity of the team to obtain and bank primary AML/MDS samples.

The team is well connected to a number of national groups (GOELAMS, Groupe Français de Myélodysplasies) or other networks (GReX labex, SIRIC: Site de Recherche Intégrée sur le Cancer).

- Weaknesses and threats:

- Relative lack of international networking and valorisation,

- Lack of appropriate in vivo models especially xenotransplant,

- Two leaders for one team, each of them with an expertise and project different from the other. This governance can be synergistic but may also lead to a "two teams in a team" situation".

- Recommendations:

- It will be important that the merger with the incoming team will occur quickly and smoothly since many projects involve members from the two previously distinct teams,

- More emphasizing on the development of ex vivo long-term culture technique of primary AML/MDS as well as xeno model should be a focus of the group in general,

- Precise governance strategy.

Team 15 : Oncogenesis of digestive epithelia

Name of team leader: Ms Christine PERRET

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3 (2.3)	4 (2.8)	4
N2: Permanent EPST or EPIC researchers and similar positions	3 (2.7)	2	2
N3: Other permanent staff (without research duties)	3 (2.7)	3	
N4: Other professors (PREM, ECC, etc.)		2	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2	2
N6: Other contractual staff(without research duties)	2	1	
TOTAL N1 to N6	13	14	8

Percentage of producers	*100 %*

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	4	
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	5	6

• Detailed assessments

Assessment of scientific quality and outputs

The scientific output of this research team is excellent. The team has made essential contributions to the understanding of the biology of liver and colorectal epithelia and has produced over fifteen papers in top quality journals with first/last authorships. Research is focused on Wnt/b-catenin signaling in the turnover of intestinal epithelia and intestinal carcinogenesis (papers in Proc Natl Acad Sci USA, Gut and Gastroenterology). Moreover, the role of this signaling system in key aspects of liver pathophysiology, such as embryonic liver growth, the control of hepatocyte proliferation and inflammation-associated hepatocarcinogenesis, has been characterized (papers in Hepatology, J Hepatology and J Clin Invest). The team has performed essential work on these subjects in research periods before 2007, and the lab is internationally well known.

In the recent funding period (2007-2012), the team has shown that Wnt/b-catenin signaling is essential for Paneth cell fate determination (Dev. Biol. 2008). This was followed by the recent finding that Paneth cells are not essential for Lgr5+ and Bmi-1+ stem cell maintenance in the intestine (Proc Natl Acad Sci USA 2012). This is seminal work, as others, world-class labs, had suggested the opposite. The controversy has since been resolved, and all labs now agree with the team's findings. The PNAS paper showed that in intestinal Math1 knock-out mice, Paneth cells of the intestine are completely lost. Despite of this, intestinal crypt architecture was maintained, and stem cell markers Lgr5, Olfm4, Ascl2 and Bmi-1 remained expressed. Also, the Wnt ligands Wnt3, Wnt6 and Wnt9 that are produced by Paneth cells, were completely lost. Nevertheless, Math-mutant crypts in organ culture required exogenous Wnt ligands for proper growth and differentiation. Moreover, adenomas generated in the absence of the tumor suppressor gene APC were correctly formed in conditional Math1 mutants. These important findings show that other cells than Paneth cell, for instance mesenchymal cells, may provide Wnt and other essential growth factors for the generation and maintenance of intestinal stem cells.

In the liver, it was found that Wnt signaling plays essential roles in fate determination of hepatoblasts, in inflammatory responses, and in the metabolic zonation along the porto-central axis (J.Clin. Invest. 2012). In hepatocellular proliferation, TGFa was found to be a target of b-catenin (Developmental Cell 2006). b-Catenin mutations are associated with a particular metabolic profile (J Pathol 2007). In very recent work, it has been shown that the LKB1 and NR pathways appear to be involved. Quantitative proteomic analysis using 2-D DIGE and MS have demonstrated that b-catenin signaling induces a shift in glucose metabolism from oxidative phosphorylation to glycolysis (Warburg effect) (Proteomics 2009). More recently, genome-wide Chip-seq/RNA-seq analyses have been used to examine the mechanism of these changes, and the nuclear receptors AhR and CAR seem to be involved. The lab has also compared Axin1 loss-of- andbcatenin gain-of-function mice, and shown that liver tumorigenesis is entirely different in these two mutants (Oncogene 2007).

Assessment of the team's academic reputation and appeal

The team leader is a highly-respected scientist and an expert in Wnt/b-catenin signaling, both in the fields of gastrointestinal tract and liver biology. The other senior scientists in the team are also excellent scientists, who have proven their capacity to lead top quality research. These scientists are frequently invited to participate as speakers to relevant meetings, and contribute to well recognized international congresses of the fields. Several National awards have been conferred to members of the team. Numerous collaborations with French national teams and international laboratories, e.g., the Clevers lab in Utrecht, have been conducted.

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

The report indicates interaction with the industry during this period. This was focused on the application of the experimental mouse models developed by the team.

Assessment of the team's organisation and life

The unit shows a compact and well coordinated organisation. Although there were different project leaders, their interaction with the team leader appears to be smooth and productive. This is also demonstrated by the substantial funding of the teams activities obtained from public sources in highly competitive calls. It is important to note the successful involvement of a pathologist, who brings essential and unique expertise into the team.

Assessment of the team's involvement in training through research

Four PhD theses have been defended during this period. There are also other four theses in progress. Four master's degree students have been supervised. Some members of the team also participate in undergraduate teaching. These are reasonable figures for the size of the team.

Assessment of the five-year plan and strategy

By the work listed in the scientific reports, the team has set the foundation to be successful in the future. The five-year plan and strategy are based on the scientific excellence of the team. Objectives are centered around the role of the Wnt/b-catenin signaling in differentiation and transformation of liver epithelial cells, as well as in intestinal homeostasis. The research focus is well chosen and will yield important new insights into signaling networks in development and cancer. These studies are also the basis for the development of future therapeutic interventions. The expertise of the team is clearly projected in the clear-cut definition of these objectives. The means to achieve these objectives are perfectly within the reach of the team. The planned experiments present logical extension of the ongoing studies and will result in important results.

Conclusion

- Strengths and opportunities:

The team is internationally recognized as leaders in the field.

They have established important national and international collaborations.

They propose a multidisciplinary approach in this project. The implementation of state-of-the art techniques (genomic, metabolomic and clinical studies), together with their expertise, guarantee the viability of the project.

The funding is excellent.

- Weaknesses and threats:

This is a highly competitive field.

The number of post-docs (2) is perhaps low for the workload proposed.

- Recommendations:

The team should attract more post-docs, in particular international post-docs.

The Wnt/beta-catenin pathway is a key signaling system dysregulated in liver and colon cancer development. This pathway is intrinsically difficult to manipulate, its druggability is proving complicated. However, perhaps this team is among the best positioned groups in the world to participate in studies leading to the development of Wnt/beta-catenin targeting agents. They should exploit this advantageous position in interaction with the pharmaceutical industry. This would result in important additional funding for their research, and ultimately in the development of therapies that could benefit cancer patients.

Team 16 : Gene expression, Development and Disease

Name of team leader: Mr Marco PONTOGLIO

Workforce

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

Percentage of producers	*100 %*

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	1	
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	1	2

• Detailed assessments

Assessment of scientific quality and outputs

The team has a long-standing interest in the function of HNF1 alpha and beta genes. They focused on function of both transcription factors in the intestine, the role of HNF1 beta in kidney development and cyst formation as well as modifier loci affecting diabetes onset in HNF1 alpha knockout mice. Their results indicate globally that HNF1alpha and beta play important functions in the morphogenesis and differentiation of epithelia in the different organs. The results obtained are impressive and a high publication output in journals including Nat Genet, Nat Med, PNAS, and Development was also reflected as highlights from Cochin Institute publications. The group works at the cutting edge between sophisticated mouse models that allow to get molecular insights from a complicated genetics originating from human disease. Here, a number of disease models have been established relevant for multiple genetic human disorders that cause severe developmental abnormalities even associated with abortion or organ malfunction causing premature death. Thus, the work of the team is truly translational and has addressed in the last years the relevant questions and built state-of-the-art models to answer this questions.

Assessment of the team's academic reputation and appeal

The group has a high international visibility and excellent reputation, which is reflected in the quality of peer reviewed publications and in the number of presentations given in international conferences. Funding is secured from several national sources (FRM, Bettencourt Schueller, ANR) as well as European collaborative work (FP7). Overall, the participation of the team leader in several significant network grants with international visibility brings in third party grant money to Cochin, which strengthens also the technology access and provides reflection of the teams research activities on an international level. A current database search on Cited Reference Search (ISI Web of Knowledge) for the PI reveals that his publications achieve an increased citation number over time, which reflects outstanding publications that get cited over longer time. The Average Citation is 42, which the evaluators call excellent.

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

The team has several collaborations within the Cochin Institute, with partners in France, and worldwide. They contribute to the "WHO am I" Labex excellence program, and EU FP7 "Syscilia" and EU FP7 Marie Curie "TRANSCYST" networks.

Assessment of the team's organisation and life

There are no specific remarks to this point and the team is very well integrated at Cochin, best reflected by the leadership of the PI as department chair.

Assessment of the team's involvement in training through research

In the evaluated period, one PhD student finished successful his studies and obtained a post-doc position at Harvard University. Three more PhD students are currently integrated in the team and two more will be recruited. With two post-doctoral researchers present and two to be hired, two senior researches (CR1) and the team leader (DR) present, this seems an excellent balance for teaching and transmission of obtained skills. Moreover, the PI is involved in several lecture teaching courses, which seems justified and not taking too much of his time as a research investigator and manager.

Assessment of the five-year plan and strategy

The proposal for future research outline is clearly written and structured. The project has a well balanced mix of state-of-the-art mouse models with a clear relevance to human disease. The proposed experiments are a logical continuation from the obtained results. In a first project, they will investigate how HNF1beta stays associated to mitotic chromatin and which epigenetic marks might be associated. The second project is designed to further understand the role of HNF1beta in the mouse kidney and MODY 5 patient material, which is also of obvious clinical relevance. The third part of the project will deal with modifier genes for diabetes risk in HNF1alpha deficient mice. One genomic region has been already identified, which contains 10 genes carrying non-synonymous SNPs between resistant and sensitive mouse strains. These are very ambitious projects integrating developmental biology, molecular and cellular biology, genetics, genomics and bioinformatics. The PI is fully aware of the ambitious character of the projects. With two additional post-docs to hire and collaborations with the bioinformatics department (Paris 5 University) for large-scale data analysis and Strasbourg University for the identification of modifier genes for the diabetes risk in HNF1alpha deficient mice, the projects seem realistic. The diabetic modifier locus once narrowed down could be considered to be floxed to generate monoallelic deletion or duplication for further gene dosage questions.

Conclusion

- Strengths and opportunities:

This is a well-built team with the proposed research continuing from recent very interesting observations. The research project combines multiple levels from molecular and cellular biology to in vivo mouse development studies and analyses of patient material. Several large scale approaches combined with bioinformatics analyses are planned in addition.

- Weaknesses and threats:

A threat of limited animals space at the Cochin institute is overcome by collaborating with the group in Strasbourg and partially performing the animal experiments there. However, the Cochin Institute should ensure sufficient transgenic animal housing to facilitate daily work. An additional problem could arise from the large amounts of data generated that for follow-up, verification and confirmation experiments simply the resources could become saturated. Planned creation of additional cell culture space and acquisition of microscopes should overcome the problem. The team is very active for epigenetic profiling, ChIP-seq or in deep sequencing. The team collaborates here with the bioinformatics team of the University, but limitations in bioinformatic support are a threat for all research units that carry out large sequencing projects. Collaborating here with the bioinformatics team at the University might be of interest to the Institute Cochin, which should support such collaboration.

- Recommendations :

The studies should be performed as proposed.

The Cochin Institute should provide more animal space.

Team 17 : Genomics, Epigenetics and Pathophysiology of reproduction

Name of team leader: Mr Daniel VAIMAN

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	6 (4.7)	7 (4.3)	7
N2: Permanent EPST or EPIC researchers and similar positions	12 (9)	11 (7.7)	11
N3: Other permanent staff (without research duties)	5 (4.8)	5 (4.3)	
N4: Other professors (PREM, ECC, etc.)	1 (-)	1 (-)	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1 (0.5)	1
N6: Other contractual staff(without research duties)			
TOTAL N1 to N6	25	25	19

Percentage of producers	*100 %*

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	7	
Theses defended	15	
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	14	14

• Detailed assessments

Assessment of scientific quality and outputs

The team has made significant progress in the field of reproduction diseases both in gamete formation /interaction, endometriosis and placenta diseases (preeclampsia).

Altered gene expression in preeclampsia has been shown to be related to epigenetic mechanisms. Functional interaction between TAT1 and CFTR proteins have been shown to be involved in sperm motility and capacitation. Inter membrane oocyte-spermatozoa forces were measured by Bio Membrane Force Probe assay. A unique mouse model for severe preeclampsia was generated. The development of this mouse model (overexpression of STOX1) will allow new investigation proposals.

The team has a real national and international outlook. The mouse model will help to increase this outlook.

130 publications in peer reviewed jounals from 2007. The 5 major articles have been published in Human Molecular Genetics (3), PNAS (2).

Assessment of the team's academic reputation and appeal

At least 7 international invitations.

The team has attracted a young newly recruited researcher (CR2 Inserm) and 2 engineers.

The team has been accepted as a part of selective structures (DHU "risk and pregnancy"; LABEX "who Am I"; IDEX Sorbonne Paris Cité).

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

Regular contribution to TV scientific programs (E=M6).

Contribution to "le magazine de la santé".

One patent.

Assessment of the team's organisation and life

The team is well structured to work on fundamental and clinical aspects in relation with human reproductive diseases due to its composition (basic researchers and clinicians).

Assessment of the team's involvement in training through research

Since 2007, 15 PhD theses were defended.

Teaching to professionals: workshop at Inserm on epigenetics and ChIP.

Assessment of the five-year plan and strategy

The team is sturctured to work in the field of human reproductive diseases including spermatogenesis defects, placental disorders and endometriosis. In the context of male infertility, 3 points will be investigated:

The epigenetic mechanisms underlying the spermiogenesis process leading to infertility will be studied in Sly-deficient mice. This part of the project will include translational approaches based on the use of testicular tissues (CECOS, JP Wolf).

Studying the interaction between TAT1 AND CFTR (Cystic Fibrosis Transmembrane Conductance Receptor) appears to be an original approch in the context of ion fluxes and asthenospermia.

Gamete interaction using video microscopy FRAP and confocal image analysis. The aim of this part of the project is to investigate the interaction between the Cd9 tetraspanin and the cytoskeleton through Ezrin-Radixin-Moesin proteins.

While the four points of the project are interesting, the point 1 theme appears original and well funded (ANR2012-2016 Mucofertil). The point 2 is also original but still at its beginning (EPIEFXY). The point 3 subject related to gamete interactions is interesting. However some clarification remained needed concerning the experimental models (i.e. which germ cell line model for siRNA transfection experiments ?) as well as the funding.

Beside gamete formation and interaction, uterine diseases such as endometriosis is one of the other major causes of infertility. The aim of this part of the project was the constitution of an extensive collection of samples from affected patients. Whole genome approaches have been used to characterize these pathological tissues: transcriptome, methylome and GWAS (by a DNA pooling approach). Two interesting observations were reached: identification of DNMT3L polymorphism associated with endometriosis and IL33 as a potential new circulating biomarker. The involved PI is well recognized in the endometriosis field.

It is now planned to identify and study the putative interacting proteins with DNMT3L. This part of the project is funded by AGREGOF (the cost is not indicated). The number of people involved appears low. This may represent a limitation for the team of the part of the project.

The third and last part of the project is devoted to placenta diseases including imprinted genes and preeclampsia. The team has identified three genes whose expression is deregulated through epigenetic (methylation) mechanisms (TBX15, Cul7/Cul4B, SerpinA3) mainly by using human samples and cell cultures. One of the major original aspects in this project is the obtention of an animal model (mouse model overexpressing the human STOX1 gene). This will allow interesting international collaboration and (thus) more fundings.

Together this project associates several aspects of reproductive diseases. The main theme is clearly related to preeclampsia besides two other themes respectively related to gamete formation/interaction and endometriosis.

Concerning the theme gamete formation/interaction, it appears clearly that this part of the project related to TAT1/CFTR is scientifically interesting and robust (personal, funding).

Conclusion

● Strengths and opportunities:

- Broad approach of the infertility diseases,

- basic and clinical research with appropriate personnel from research institutes (Inserm/CNRS/University) and from hospitals,

- substantial funding (at least for spermatogenesis),

- Important and relevant collaborations,

- good quality of supervision and follow up of PhD Students,

- the implantation in the Cochin Institute provides adequate expertises and technologies,

- the team is accepted as a part in DHU, Labex and IDEX structures.

● Weaknesses and threats:

- Placental diseases in the central theme.

The generation of a relevant experimental model for preeclampsia is interesting and original. This theme suffers of a lack of important funding. This could be, as indicated by the team, improved by incorporation into the DHU and LABEX structures.

- for the themes related to gamete formation/interaction, the fundings exist but probably there is a need for more personnel to reach the objectives.

3/ endometriosis: the fundings and the personnel devoted to this theme should be clarified.

● Recommendations:

More funding for placenta disease and more human ressources for the other themes particularly those related to gametogenesis/interaction. If not possible, then, with time, the team will have certainly to make choices and prioritize certain themes.

Team 18 : Virus intracellular trafficking

Name of team leader: Mr Serge BENICHOU

Workforce

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

Percentage of producers	*100 %*

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	6	
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	2	1

• Detailed assessments

Assessment of scientific quality and outputs

This team has carved out a very respectable international reputation in the molecular cell biology of HIV-1 infection. Their constant progress in understanding the diverse molecular interactions between HIV-1 accessory proteins and host cell machinery has led to increased basic understanding of these processes and the beginnings of a translational programme in antiviral drug development. The combined fundamental/translational drive of the lab puts it in a strong position to continue into the next period. The group has had a good critical mass over the period, but this will shrink with the imminent departure of one of the PIs.

Publications have been consistently strong in very respectable specialized journals including J Virol, Retrovirology, Traffic, Blood, resulting both from internal and external collaborative projects. Nevertheless the team has not published in high impact (>10) more general journals (in this instance the Blood paper may be considered as a specialized journal).

Assessment of the team's academic reputation and appeal

This is an established group with an international reputation. It might wish to increase its visibility further by the PI and different lab members giving more seminars/meeting presentations in the USA and elsewhere, allowing further networking and exposure.

Funding appears to be at a very good level and sufficient for this quite large lab to thrive. Future funding for the Nef inhibitor project may become harder to obtain as the work becomes more developmental and less basic research.

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

The PI is member of INSERM CSS5, chairman and member of AERES committees, member of editorial board of Retrovirology and Viruses, "prime d'excellence scientifique" CNRS, secretary of the sino-french association for the development of science and technology.

The PI holds two patents and has contracts with Carlina Technologies and GSK. He participates into a program to train pupils from secondary school. In sum excellent socio-economical interactions.

Assessment of the team's organisation and life

The group will shrink as the other co-PI leaves the lab.

Assessment of the team's involvement in training through research

The PI is co-organizer of a Master 2. He teaches several hours in masters in France and Belgium, and at the School of Industrial Biology. Six PhDs (3 for each PI), 2 M1 and 2 M2 were obtained in the lab. The 6 PhD students that graduated obtained positions: 3 post-docs in France, 1 post-doc in Norway, 1 CR2 CNRS, and 1 scientist in a biotech.

Assessment of the five-year plan and strategy

1. Fundamental research into Nef function has resulted in a strong understanding of mechanism and cell molecule interactions, and this has led to development of Vhh-type inhibitors that may be of use either as direct inhibitors if delivery can be managed, or in screening for small molecule inhibitors. However the ultimate utility of such inhibitors remains to be established.

2. There is a decision to focus less on Vpr and Nef function in T cells, and more on their function in macrophages. A new project is proposed to investigate their function in macrophages, particularly during cell-cell spread of HIV-1 from T cells to macrophages. This will be complemented by a full cell and molecular biology analysis of T cell to macrophage viral transfer. Other groups are already working in this area, and so the group will need to be efficient to avoid potential problems of direct international competition.

Conclusion

- Strengths and opportunities:

A strong long-term focus on HIV-1 virulence factors has been fruitful in generating strong incremental advances in understanding HIV-1-cell interactions. The combination of molecular virology and cell biology techniques is a powerful approach to probing immune cell function in health and disease.

- Weaknesses and threats:

The group lacks a particular 'flagship' study for the 5 year period, and this is evident in the absence of a high-impact publication. Whilst this is not in itself cause for concern as the rate of progress has been very strong and steady, the group might like to consider in which area they could make a major contribution in the next period, and focus their efforts in this direction. For future studies, the PI needs to decide how much emphasis will go into the Nef inhibitor project, as this may become a drain on time and resources for what is essentially a drug development project. The macrophage project is interesting and has good potential for a future project that includes molecular and cell biology of HIV-cell interactions. The small size of the team may make it vulnerable, although it appears that a new staff member is likely to be recruited in the near future.

- Recommendations:

More interaction with other members of the Cochin Institute would be advisable as there are clear potential areas of synergy, such as (eg.) collaboration for live cell imaging in tissue slices and perhaps more precisely defined interactions with groups for macrophage work. Similarly, international collaboration with the murine BLT model might lead to intravital analyses of HIV-1 spread between macrophages and T cells.

Team 19 : Host-virus interactions

Name of team leader: Ms Clarisse BERLIOZ and Mr Stephane EMILIANI

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2	2	2
N2: Permanent EPST or EPIC researchers and similar positions	2	2	2
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.)	4	5	5
N6: Other contractual staff (without research duties)	1	1	
TOTAL N1 to N6	11	12	9

Percentage of producers	*100 %*

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

• Detailed assessments

Assessment of scientific quality and outputs

The recent research focused on the characterization of the interactions between cellular and viral proteins during the different steps of HIV replication that enable the formation of viral particles.

Major achievements of this research deal with :

(i) the identification and functional validation of cellular cofactors controlling nuclear import and integration of the viral genome into the chromosome of the host cell,

(ii) the identification and characterization of viral components trafficking to assembly sites, the budding and release of viral particles and their maturation.

The group has good evidence for sharing resources and technology but less obvious evidence for intellectual and creative synergy in their scientific projects. Particular success is evident in the work of CBT relating to cellular components required for optimal HIV replication. The impact of the published work appears to be increasing over time, suggesting that this group is increasing its international visibility and impact. The quite large group gives a critical mass for maintaining momentum into the next period. The discovery of several new cellular partners important for HIV-1 replication, particularly during stages of nuclear import and integration, has been important to the field. The synergy between the PI and co-PI is not evident from the publication record, however other types of synergy exist between the groups such as sharing resources, meetings etc.

The team has a strong recent publication record with papers in specialized but high impact journals such as Plos Pathogens, Traffic, Retrovirology. It also got several publications in high profile journals (Nature, PNAS, EMBO J), but mainly through collaborations. The overall output is very respectable.

In summary, the team has issued strong papers in more specialized journals revealing high impact international recognition. An obvious flagship paper in a major journal would be a bonus in the future.

Assessment of the team's academic reputation and appeal

The group is well established and well recognized worldwide. It might wish to increase its visibility further by giving more seminars/meeting presentations in the USA and elsewhere, allowing further networking and exposure.

The funding appears adequate and should not be rate limiting for future progress.

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

The team has established very strong links with industrial partners (eg 3 international patents, and tight research collaboration with an industrial partner. The team has trained 3 engineer technicians from this partner.

Assessment of the team's organisation and life:

Recruitment of young talented researchers will certainly strengthen the team.

Assessment of the team's involvement in training through research

4 PhD theses were successfully completed; 2 further PhD projects are in progress. 2 M1 and 5 M2 students have been supervised.

Assessment of the five-year plan and strategy

The main research axes in the coming years deal with :

1. the discovery of cellular molecules with roles in early (nuclear import, integration, transcription) HIV infection. LEDGF, TNPO3, VBP1.

2. the discovery of cellular molecules with roles late in HIV infection (assembly, Env incorporation, budding).

Both sets of projects are based upon a systematic and careful discovery program with rigorous characterization and follow up on function.

3. the targeting of HIV-cell molecular interactions for therapeutic purposes, with a particular focus on LEDGF and INT interactions leading to loss of integration. This research part has already led to some preliminary success.

Conclusion

- Strengths and opportunities:

The combination of strong biochemical, molecular biological and cell biological expertise means that this group has a very powerful toolkit for attacking questions associated with virus-cell interactions. They are using this toolkit to address questions of importance to the biology of HIV-1 replication and to the potential for translational research into antiviral drugs targeting early/late (eg. LEDGF/Tip47) cellular partners for essential viral functions. A strong collaboration with an industrial partner is a positive point. The lab has a great energy and momentum, and clearly has excellent direction and originality in novel interactions discovery. The partnership between the two group leaders is a clear strength, and even thought they do not share the same molecular targets, the strategies and approaches are shared, as are intellectual processes such as lab meetings.

- Weaknesses and threats:

The lack of clear synergy from the partnership may be a concern in the long term, and may be addressed by ensuring joint projects leading to joint publications.

- Recommendations:

The team should maintain its strong momentum whilst considering the research questions to address with the highest priority for the next period. There is a clear democracy within the group in that everyone has their own project. This is a strength, but also may lead to dilution and dispersion of effort. The group should make sure that they maintain sufficient flexibility and power to prioritise their efforts when necessary to build the highest originality projects into high-impact papers. The sub-teams should join forces in a more overt manner and seek synergy as much as possible. Setting up shared projects is a strong recommendation. Some thought might be given to future collaborations with other members of the institute. The group could have had more international exposure, particularly in the last 3 years. Perhaps more presentations at international meetings would be good.

Team 20 : Mucosal Entry of HIV and Mucosal Immunity

Name of team leader: Ms Morgan BOMSEL

Workforce

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

Percentage of producers	*100 %*

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

• Detailed assessments

Assessment of scientific quality and outputs

The team leader has worked on mucosal HIV-1 transmission for many years, showing an admirable focus and persistence with a single very important research question. Her work has in many respects led the field in terms of promoting viral trancytosis and its prevention by mucosal antibodies, the induction of mucosal antibodies by vaccination, and the mucosal functions of antibodies apart from virus neutralization. She now resolutely works with the most physiological in vitro models of in vivo HIV-1 transmission, models which are complicated to establish and work with but which come as close to real biological relevance as possible. Her vaccine work with biotechnology company appears to be extremely exciting and has led to a successful Phase I clinical trial. She should be congratulated on her courage to pursue this research in the face of strong international competition.

The obvious stand-out paper in terms of impact is the 2011 Immunity paper describing the efficacy of the gp41-based vaccine in macaques. However, other studies relating to tissue models of HIV-1 transmission (Plos Pathogens) and antibody functions (PNAS) are very well published. Given the modest size of the group the publication output of the lab is impressive. This level of publication is set to continue into the next period.

In summary the output grade is excellent, with some very strong papers in high-impact journals, and several strong papers in specialized journals. The team has made a strong and respected research niche for itself.

Assessment of the team's academic reputation and appeal

The team leader has a strong presence in the international HIV pathogenesis and vaccine communities. Considering the small size of the group, this is an excellent profile.

National funding seems to be fine and unlikely to be a limiting factor for future progress. However it was unclear to the referees whether the contract with the biotechnology company will continue into the future.

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

The team has issued three patents, has taken part in one phase I clinical trial, and made several interventions in local media.

Assessment of the team's organisation and life

The committee has no particular comment regarding this point.

Assessment of the team's involvement in training through research

The team has a good training activity : 2 PhDs, 2 M1 and 2 M2 were successful.

Assessment of the five-year plan and strategy

The projects planned in the coming years deal with :

1. Physiopathological studies in models for mucosal transmission of HIV-1. The studies planned are original and competitive, are supported by good papers and a strong presence in the field. In this regard, recent work in the male mucosal tissue field appears particularly strong, imaginative and novel.

2. Development of a mucosal vaccine against HIV-1 infection. This part stems from exciting results with the first challenge study, which are being repeated. There might be some difficulty to move forward into a Phase-II trial.

Conclusion

- Strengths and opportunities:

The PI is an original thinker, who despite limited resources and manpower consistently produces interesting ideas and new paradigms for study. She does not follow the general trend so often set by our USA colleagues, but cuts her own path showing innovation and taking risks. She is focused and persistent in understanding mechanisms of HIV-1 transmission across mucosal surfaces. The combination of basic and translational research is a powerful means to contribute maximally to the field.

- Weaknesses and threats:

There are few obvious weaknesses, perhaps that with a small group there is always a risk of being scooped by international competitors. It is uncertain how the vaccine project will evolve over the next 5 years with the stated issues over funding.

- Recommendations:

Work on in vitro models of HIV-1 transmission are world-leading and ought to be fully supported. The mucosal HIV-1 protective vaccine study appears to be very exciting in its protective efficacy, and indeed shows probably more promise than any other current approach. Although difficult, she should persist in attempting to get this result promoted, confirmed elsewhere, and if possible taken into a Phase II trial. Has the PI considered applying to the NIH for funding to take her gp41 vaccine further ?

Team 21 : Vascular Cell Biology in Infection, Inflammation and Cancer

Name of team leader: Ms Sandrine BOURDOULOUS

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1	2 (1.1)	2
N2: Permanent EPST or EPIC researchers and similar positions	1	2 (1.5)	2
N3: Other permanent staff (without research duties)	1	1	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	6	3	3
N6: Other contractual staff (without research duties)		1	
TOTAL N1 to N6	9	9	7

Percentage of producers	*100 %*

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

• Detailed assessments

Assessment of scientific quality and outputs

The team is headed by two PIs who have both strong expertise in the field of adhesion molecules that govern vascular plasticity. The team is reinforced by the presence of the current director of Cochin Institute, an international leader in the field of brain endothelium and the director of the labex Neurovasc. The team focuses on how vascular homeostasis is jeopardized by pathological signals. They develop research in the field of Meningococcal infection, infection with Kaposi sarcoma herpes virus and interaction between endothelial cells and cancer stem cells in brain tumor. In addition the team develops work on the generation of anti-HER2 inhibitors in an attempt to valorize this work. The team published in the past years some good publications and have a good track record.

The team has made important contributions to the understanding of how endothelial cell functions are modulated by inflammation- and infection-driven signals, especially at the BBB (Blood Brain Barrier). They found that VEGF induces internalization of VE-cadherin and unravelled the mechanism. The work on the effect of a viral and a bacterial pathogen on the breaching of the endothelial barrier has led to the identification of a novel leukocyte adhesin molecule. The team has also found that infection with *N. meningitides* induces recruitment and phosphorylation of ErbB2 and prevents ligand-independent activation. This has implications in the understanding of aggressive breast cancer. A patent has been applied.

Finally, an in vitro model of glioma cells with brain endothelial cells has been developed, and their interactions have been investigated.

The team has published between 3 and 6 international papers per year, a total of 31, 14 of which as leading authors (first and/or last author). Papers were published in good cell biology, microbiology or oncology journals (including J. Cell Sci., EMBO Rep., Oncogene, Mol. Cell. Biol., Nat. Rev. Microbiol., Nat. Cell Biol., J. Cell Biol.), as well as one paper in Science, one in Cell and one in FASEB J. However, for the two papers in the highest impact journals, the team members were not leading authors. Alltogether the scientific output is very good.

Assessment of the team's academic reputation and appeal

The committee notes the recruitment of one MCU-PH with an expertise in the biology of meningococcal infections and a new PI. This underlines the attractivity of the team. In addition the presence of the head of the Institute, who is very well recognized in his research field, is important for the international vision of the team. We also note the presence of 4 post doctoral scientists. This is an important point for the development of the team.

The team leader is young and dynamic. International recruitment of postdocs demonstrates the attractivity of the team. The team is integrated in a Labex which could provide some financial support. The capacity to raise funds is also good (grants from FRM, ARC, ANRS Marie Curie).

Collaborations are essentially at the national level, and most seminars have been given in France. There is limited international exposure, although there have been presentations at international meetings. There is no international grant.

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

The team has applied for 2 patents in 2011 and 2012. The team leader has given two lectures at the Claude Monet High School in Paris. One of the scientists has been a lecturer for FRM donators, and has delivered several interviews.

Assessment of the team's organisation and life

It is not clear how the team is organized. It looks more like the two PIs have rather independent projects, due to two different pathogens on the same endothelial cell barrier.

Assessment of the team's involvement in training through research

The team has a good post-doctoral training activity (currently 7). They have trained 3 PhD theses, and currently train 4 additional PhD students. In addition, the team has trained 9 M1 and 4 M2 students.

Both senior scientists have been in thesis committees and are involved in teaching M1/M2, as well as in a DU in Microbiology in Lille.

Assessment of the five-year plan and strategy

The team develops 4 themes. The aim is to decipher the mechanisms by which pathogens and tumor cells establish interactions with endothelial cells and generate vascular remodeling. The project will investigate the role of CD146 and the ß2 adrenergic receptor in N. meningitidis infection, they also test the role of GPCR in the oncogenesis induced by Kaposi sarcoma herpes virus. In addition, they will test interaction between cancer stem cell and endothelial cells in glioma model. Another project involves the generation of drug that blunt HER2.

The team is a merger of two previous teams with the addition of a MCU-PH and the participation of the director of the Cochin Institute. There is good complementary expertise. All technologies are available. Good collaborations will guarantee the successful outcome of the project. Although the third project makes use of original culture systems, and the strategy looks sound, this looks like a side project.

Conclusion

- Strengths and opportunities:

The interaction with clinicians in the field of meningococal infection and glioma is important. Past publications from the team or in collaboration underline the capacity of the team to generate good science in the two fields. The programs on the molecular biology of Kaposi sarcoma and glioma are well described and very innovative with a link with translational research and may lead to important discovery.

The team is composed of members with good complementary expertise. All have a good publication record and have been able to secure national funding. The team is part of a LabEx. It makes use of well-mastered and available technologies. Some of the material is uniquely available (e.g. human brain endothelia cell line). Good and well-established collaborations are an important asset. The research subject chosen is of great medical importance. The project has a very good potential, both with respect to basic findings and with respect to potential medical applications.

- Weaknesses and threats:

The work on HER2 is not in the scope of the team and very competitive. The team has no past history in the field of cancer research and little collaboration with clinicians involved in breast cancer treatments. The team is rather small (2.6 senior scientist FTE), and the project is very ambitious.

There is limited international visibility, no international grant, no participation in European Networks.

- Recommendations:

The five year program is very good. The 3 programs are well designed with good preliminary data and publications. The work on Her2 may not be the core of the program. The fundamental impact of this work is minor in addition the development of new therapy on HER2 overexpressing cells is very competitive and may be very difficult with the recent development of pertuzumab and TDM1.

It may be advisable that the team focuses on the most advanced projects. Also, it may be useful to better integrate the two "infection" projects by true collaborations (e.g. both infections target a GPCR).

It would be good to increase international visibility by participating to international networks and applying for international grants.

Team 22 : Cytokines and viral infections

Name of team leader: Mr Rémi CHEYNIER

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2 (1.5)	2 (1.5)	2
N2: Permanent EPST or EPIC researchers and similar positions	1 (0.4)	1 (0.4)	1
N3: Other permanent staff (without research duties)	2 (1.9)	2(1.9)	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2	2
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	7	7	5

Percentage of producers	*100 %*

	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	2	
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	2	2

• Detailed assessments

Assessment of scientific quality and outputs

This team, which was created on January 2010, results from the recent merging of 3 tenured researchers, the team leader being a former PI from Pasteur Institute. The team addresses several questions dealing with the consequences of viral infections on cytokine responses and the role played by these cytokines on infection control and pathogenesis.

Among the main contributions of the team can be mentioned several results showing that :

(i) IFNa therapy impacts on thymopoiesis and is associated with decreased plasma IL17 concentration in HCV-infected patients,

(ii) the lymphopenic effects of IFNa can be counteracted by rIL7 in SIV-infected macaques. However this cytokine can also favor infection of recent thymic emigrants, thus hampering its use as an immunotherapeutic agent in this setting,

(iii) type I IFN subtypes can have distinct effects on DN thymic differentiation and viral replication. Importantly the IFN subtypes primarily produced in vivo are not the most potent to inhibit viral replication suggesting inadequate IFN responses,

(iv) IL7 can be a potent adjuvant for mucosal immunity, a quite unexpected and highly original observation,

(v) prophylactic HPV vaccination of men could prevent HPV16 infection and transmission to their female partners, based on analysis of anti-HPV16 E2-specific T cells in a small patient cohort.

These various studies have led to regular publications in good specialty journals either as leading authors (Plos One, AIDS, 2 Blood, Clin Exp Immunol, letter in N Engl J Med...) or as collaborators (Blood, JI, Plos One...).

Assessment of the team's academic reputation and appeal

The team has established a very good network of international collaborations, with teams in Portugal, Belgium, US, Canada..., and has been strongly implicated in ANRS meeting organisation. The team leader has been invited at several international meetings, and has shown a very good fund raising activity during recent years, with several grants obtained from ANRS (520 k€ since 2005), Marie Curie call and industrial connections (80-140 k€/yr support during the last 5 years).

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

The team leader has established strong and long lasting interactions with an industrial partner (2 CIFRE grants, postdoctoral fellowship and research contracts (ibid), and has been involved on a regular basis in evaluation committees (in particular from ANRS). Most studies have a strong translational component and show significant clinical implications. One PI from the team has issued several licensed patent on lipopeptidic vaccines.

Assessment of the team's organisation and life

The team recently joined the Cochin Institute and comprises 3 tenured researchers that used to work independently before. While there is a trend for better integration of the research topics dealing with HIV and HPV, it is too early to assess the added value of this recent merger. Nevertheless the team has been able to rapidly establish strong and relevant collaborations with several other teams in Cochin that show complementary expertise in HIV.

Assessment of the team's involvement in training through research

Good training of PhD students (2 got their PhD thesis during the last two years and 4 students joined the team meanwhile).

Assessment of the five-year plan and strategy

Three main lines of research will be pursued in the coming years :

(i) analysis of local IFNa subtypes in SIV-challenged macaques and assessment of the IFNa subtypes best suitable for antiviral therapies. This project should benefit from logical collaborations with team 25, who will bring complementary expertise on dendritic cells.

(ii) characterization of cytokines contributing to mucosal antiviral immunity in macaques. This part stems from original findings from the team suggesting a new role for IL7 in boosting mucosal responses, and will be extended to broader analysis of cytokines and chemokines involved in mucosal immunity against SIV, HIV and HPV. Thanks to connections already established with the industrial partner, this program will allow assessment of IL7 as an adjuvant for mucosal vaccines in rhesus macaques.

(iii) more upstream studies dealing with IL7 receptor signaling and production of soluble IL7R in SIV-challenged macaques will be implemented under the supervision of the associate professor who recently joined the team.

Several of the issues addressed are sound and could have a significant biomedical impact. They should benefit from privileged access to primate facilities and patient cohorts. The research devoted to IFN and the biological/antiviral activity would deserve a careful evaluation because previous attempts in the field did not conclude to any major difference of activity for the different products of IFN genes. The priority of the current project should include both aspects, basic and applied, of the research devoted to IL7 expression during early phases or SIV infection and the use of IL7 to vaccine strategies. The research strategy devoted to IL7R deserves to be further defined. As a general recommendation, the team is encouraged to develop the more basic aspects of the project emphasizing the mechanistic aspects of this research.

There is a concern that the project devoted to the role of chemokines in HPV-induced lesions is too limited by its objectives and lacks mechanistic approaches. How the integration of this group in the team is envisaged in the future?

Conclusion

- Strengths and opportunities:

The team has a good publication output and a well recognized expertise in SIV primate studies and HIV/HCV patient immune monitoring.

IL7 is considered as an important therapeutic cytokine that could promote the reconstitution of the immune system in HIV-infected patients. The counteracting effect of IL 7 that antagonizes the effects of type I IFN expression in HIV or HCV infections offers an opportunity to investigate the molecular basis of IFN-mediated immunosuppression. Research in primates and the access to biological samples in infected animals is a rare opportunity that this team exploits. The scientific environment at the Cochin Institute is optimal as it enables collaborations and synergies with two other major groups investigating basic aspects of vaccine research (AH) or HIV-1 mucosal vaccine candidates (MB).

- Weaknesses and threats:

The project addresses too many questions, sometimes in a quite descriptive fashion, which are not yet tightly connected (although the project could help integrate the respective projects of the three PIs). It is unclear how the extensive screening of chemokines and cytokines in the various physiopathological settings will be exploited for future mechanistic or translational studies.

The research project relies largely on IL7-oriented topics. The future of IL7-based immunotherapies in HIV infection is uncertain although there is hope that IL7 can be an efficient adjuvant for mucosal vaccination. Changes in the strategy of the current IL 7 industrial manufacturer cast some doubts regarding the continuity of supply for these experiments in primates.

- Recommendations:

The team should reinforce the more basic and mechanistic aspects of the research. The IL7-driven regulation of chemokine and leukocyte homing in mucosae offers in this regard the best opportunity of the project as it covers aspect of the earliest immune response and pathogenesis and funnels rationale for the applied work focusing on IL7 as vaccine adjuvant. The IL7R-devoted research, although deserving further investigation, could be integrated in this major axis of research. The research on IFN type I expression and the characterisation of the biological activity of the different forms identified could be of lower priority.

The team has to face a possible attrition of the source of clinical grade IL17 and should find an alternative for getting access to this kind of reagent at least whilst the uncertainty concerning the supply persists.

Team 23 :

Innate immunity, toll-like receptors and variability of the inflammatory response

Name of team leader: Mr Daniel CHICHE

Workforce

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

Percentage of producers	*100 %*

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		
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

The team studies the pathophysiology of sepsis, which is an exciting and challenging area of research. This research topic is more than timely. All recent clinical trials directed at the "most promising" targets in septic patients have dramatically failed, leaving the field without any product approved specifically for sepsis treatment. The questions address one of the most demanding medical problems. The approach combines basic, translational and clinical approaches. Important achievements: a) impact of gene polymorphisms in sepsis, flu and malaria; b) sepsis-induced dysfunction focused on DCs; c) regulation of the TLR-NF-kB pathway in response to microbial stimulation; d) sepsis epidemiology.

Very good output in terms of publications : 82 original articles, 7 review articles and 6 book chapters. Regular publications in the best medical journals of critical care medicine: Am J Resp Crit Care Med (n°1, IF 11.1), Crit Care Med (n°2, IF 6.3, 16x), Intens Care Med (n°3, IF 5.4, 17x), Chest (n°4, 5.2), Crit Care (n°5, IF 4.6, 4x) and Resuscitation (n°7, IF 3.6, 4x). The team manages to publish in journals of general medicine, infectious diseases, immunology and biochemistry: JAMA, IF 29, 4x (1 main contribution, 1 comment and 2 x in study groups); J Infect Dis, IF 6.4 ; J Immunol, IF 6.0, 3x ; JBC, IF 4.8 ; PLoS One, 4.3, 3x ; Infect Immun, IF 4.2, 2x, etc. They also co-authored once on research articles in Nature Medicine (IF 28.4) and Blood (IF 10.9).

Assessment of the team's academic reputation and appeal

The team is made of 4 physician-scientists with ability to direct research, 2 PhD and 2 M2 students. The team has an excellent external visibility. It is recognized worldwide for its excellence in the field of intensive and critical care medicine and studies on the pathophysiology of sepsis. Members are regularly invited speakers (more than 40 per year) and chairmen in international meetings. The team obtained 3 awards from the European Society of Intensive Care Medicine (2x 2008 & 1x 2009), 1 from Société de Réanimation de Langue Française (2009), 1 from FECRM.

Members of the team have an important activity in networks/congresses: members of the European Critical Care Research Network, European Society of Intensive Care Medicine (ESICM, a team member was president elect & past chair of the Congress Committee), International Sepsis Forum (ISF), International Severe Acute Respiratory & Emerging Infection Consortium (ISARIC), InFACT Global H1N1 Collaboration. They organized the annual congress of ESICM (2009 & 2010) and ISF (2010 & 2011), ESICM summer conferences and "Journée d'interface INSERM-SRLF-SFAR". They co-coordinate a FP6, the 4th working group of ISARIC, the Groupe de Recherche sur la Réanimation Onco Hématologique and the AMARCAND Study Group. They obtained two PHRCs and important funds (> 1M €).

Two former members obtained outstanding positions: head of the Emergency Service from Monaco and Medical Director of R&D at Air Liquide. Four PhD, 9 M2 and 3 M1were obtained since 2007.

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

Numerous contracts with pharmaceutical companies. One of the scientists is a member of the Scientific Advisory Board of two of these companies, thereby attesting of his influence in the world of pharmaceutical industries. Another one is currently a member of the Advisory Committee on Severe Acute Respiratory Infections of the European Center for Diseases Control and of the Evaluation Committee of the INSERM Postes d'Accueil. He is a past member of the WHO Advisory Committee on Influenza & Respiratory Diseases and INSERM-SRLF-SFAR Interface Committee.

The team participates to the development of LIFE-Priority Fund, which gives a voice to patients and collects money to support research, education of caregivers, and initiatives to improve patients and families stay in ICUs.

Assessment of the team's organisation and life

There has been a well-defined strategy of development and excellent synergy of the PIs (25 papers co-authored). The team originates from an Avenir team created in 2002, and has been created through the impulsion of the two team leaders in 2006.

Assessment of the team's involvement in training through research

Four PhD were obtained since 2007, 9 M2 and 3 M1. Two PhD started in November 2012, currently 2 M2. Teaching in M2 and DIU in France and abroad.

Assessment of the five-year plan and strategy

The 5-year plan addresses important questions in the field of sepsis: 1-Genetic studies. a) Candidate gene studies of the PD-1 axis; b) GWAS in pneumonia combined to the analysis of virulence factors of *S. pneumoniae*; c) GWAS to identify genetic variants associated with effectiveness of treatment with Eritoran and recombinant APC. 2. Molecular mechanisms of sepsis induced immune dysfunction (SIID). a) Origin of DC repopulating the DC pool in septic animals. b) Transcriptional signatures of DCs in septic mice. 3. Reciprocal impact of SIID and tumor development on each other. This is a novel and original area of research, pertinent for human medicine. Tumor models have been established, confirming the feasibility of the proposed research. 4. Immunomonitoring and treatment strategies in septic patients. Follow up of mucosal-associated invariant mucosal-associated invariant, NK-T and γδ-T cells in septic patients.

Conclusion

- Strengths and opportunities:

The team is centered on 2 worldwide-recognized specialists in critical care, with a strong background in basic science. Clear synergy between the two PIs.

Two young MCU-PH and one CR1 scientists have recently joined the group, and a post-doc will be soon recruited.

The team has a very good output in terms of publication and outstanding international visibility.

The PIs have obtained numerous competitive grants and funding from agencies and industrial partners, and have established appropriate national and international collaborations to develop their projects.

There is a good balance between basic and clinical research.

- Weaknesses and threats:

The 2 PIs and 2 MCU-PH are part-time, with important clinical and representative duties.

The original contribution of the only full time scientist is not clear.

The team proposes an ambitious program, which will require important financial and human resources. The achievement will depend on the success of funding/contract (pending applications to ARC, ESCMID, FP7).

The research axes, combining basic and clinical science, are very appealing, but may also result in the dilution of the forces, with a risk of reducing output or delaying achievements.

No patents have been filed, this point could be fostered in the future.

- Recommendations:

Several projects run in parallel. Recommendation could be made not to disperse too widely the forces of the team by opening their interest to too many new areas of research. The risk of widespread research is that it will be time and human resources consuming, especially for a team composed of investigators with heavy clinical duties. The team may also consider deepening certain axes in order to increase chances to publish in outstanding journals.

Team 24 : Dynamics of T-cell interactions

Name of team leader: Mr Emmanuel DONNADIEU and Ms Clothilde RANDRIAMAMPITA

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3	2	2
N2: Permanent EPST or EPIC researchers and similar positions	4	4	4
N3: Other permanent staff (without research duties)	1(0.75)	1(0.75)	
N4: Other professors (PREM, ECC, etc.)		1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	3	3
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	12	11	10

Percentage of producers	*100 %*

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	8	8

• Detailed assessments

Assessment of scientific quality and outputs

The team is an established laboratory with international recognition. It has been actively involved in the field of T cell biology by using especially cutting-edge live imaging technologies for many years. During the past five years, the team has investigated the early signaling events involved in T cell activation and migration with a series of interesting findings. This was done at the molecular, cellular and tissue levels. The group is currently composed by 6 researchers, 1 technician and 7 docs or post docs. The former team leaders have headed the group since its beginning; both of them presently are closed to the age limit for retirement. For this reason, it is proposed that for the next 5 years, the team will be co-directed by two young PIs from the team, who have studied T cell activation and migration for more than 15 years and have been main actors of the team.

During the last years, several lines of research have been conducted in the team. The first one examined the functional contributions of T cell/APC contacts, especially those in an antigen-independent manner. An important paper published in Immunity reports a role of cAMP in AITCP (Adhesion-Induced T Cell Priming). The second one examined the link between PI3K pathway activation and FOXO1 exclusion from the nucleus, which is important in T cell growth. The third one examined mechanisms controlling T cell migration and activation in fresh murine lymph node and human tumor slices. An important paper reporting the role of CCR7 ligands in the control of basal T cell motility within lymph node was published in J Exp Med, while another one reporting impacts of tumor stromal fibers on T cell recruitment and motility was published in J Clin Invest. The last one examined the anergic state of tumor-infiltrating T lymphocytes in which an interesting contribution of PD-1 in inhibiting TCR signaling was described.

The team has been involved in 30 original publications and 7 reviews or commentaries. Among them, some are in either high profile (Immunity, JEM, JCI…) or top-level specialized journals (J Immunol, PNAS, Immunol Rev…). The team has created original research niches in very competitive areas with strong focuses on T cell activation and migration by using live imaging technologies.

Assessment of the team's academic reputation and appeal

This team is well-known at both national and international levels. The former team leaders were well recognized in their field. The new team leaders are experts with solid skills in the field of live imaging in T cell activation and migration. One of the former team leaders was recently awarded the CNRS silver medal (2011). A scientist has been recently recruited as CR1 by the CNRS. The team has organized two international symposia and actively participated to various important national research networks. The capacity of the team to raise funds has been very good (Ligue contre le cancer, ARC, ANR, F7P).

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

The team has produced several patents and contracts with a pharmaceutical company.

A former team leader has played an important role in nationwide discussions on scientific research policy. One team leader has co-organized the scientific popularization program « Apprentis Chercheurs » at the Cochin Institute in collaboration with the « Association pour la Promotion des Sciences et de la Recherche ».

Assessment of the team's organisation and life

No specific concerns, excellent synergies between the PIs from the team already established. The former team leaders have exerted important administrative functions at the Cochin institute.

Assessment of the team's involvement in training through research

Members of the team have participated in different master and PhD degree programs at Paris universities. Researchers of the team have supervised the activity of numerous PhD students and post-doctoral fellows.

Assessment of the five-year plan and strategy

In extending the previous observations, the proposed program tackles the regulation of T cell dynamics and function in time and space. Overall, the plan is interesting and well constructed, and is divided into three parts which are all timely and relevant :

(i) T cell signaling during migration. The first objective is to determine the role of cAMP and RhoA pathways duing T cells migration and polarization. The second objective is the further structural and functional characterization of antisynapse,

(ii) Role of Foxo-1 in T cells differentiation. The objectives are to describe the link between RhoA pathway and Foxo-1, and to determine the role of Foxo-1 during TH17 differentiation,

(iii) The last program will investigate the migration of T cells in tumors and lymph nodes. The first objective is to determine the role of matrix fiber and fibroblastic reticular cells in the activation and migration of T cells. The second objective is to evaluate the mechanism involved in tumor regression in TC1 model.

Conclusion

- Strengths and opportunities:

The team includes nine senior researchers organized into three subgroups and most of them are young and show complementary technical skills. The expertise of the team members in T cell physiology ranges from molecular levels to more integrated systems, which allows investigations from the regulation of the early steps of T cell activation to the dynamics of T cells in their native environments.

The presence of former group leaders in the team for a further period of time is a positive factor considering that they will share with the young generation their valuable experience.

The team has established strong interactions with many other basic research and clinical teams both inside and outside the Cochin institute.

- Weaknesses and threats:

Beside the main topics such as TCR early signaling and PI3K pathways that have made the team's identification, new directions are also proposed. Some of them are within very competitive areas (e.g., Foxo-1's functional roles) while others could be very much model-dependent (e.g., immune response in the TC1 tumor model).

- Recommendations:

It is essential that the team members keep their original outlooks and experimental approaches.

Team 25 : Dendritic cell physiology

Name of team leader: Ms Anne HOSMALIN

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2	2	2
N2: Permanent EPST or EPIC researchers and similar positions	2(1.5)	2(1.5)	2
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.)	2	3	3
N6: Other contractual staff (without research duties)	1	1	
TOTAL N1 to N6	9	10	7

Percentage of producers	*100 %*

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
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	4	4

• Detailed assessments

Assessment of scientific quality and outputs

This team is well recognized for its contributions on the antigen presentation pathways in dendritic cells and the role played by this cell subset in HIV pathogenesis. The team was recently joined by two PIs who brought their complementary expertise on the regulation of T cell memory responses by type I interferons, and the tissue-specific organization and function of B cells, which should allow a broader analysis of the mechanisms underlying immune dysregulations associated with HIV/SIV infections.

Among the most salient contributions of the team, the following studies could be mentioned :

(i) antigen cross-presentation by plasmacytoid DC, human BDCA3+ DC (homologues of murine CD8a DC) and inflammatory CD11bCD206 DC,

(ii) efficient cross-presentation of Ag from live cells and analysis of its underlying mechanisms,

(iii) induction of potent memory CD8 T cell responses by type I interferons,

(iv) several immune alterations associated with HIV/SIV infections such as enhanced mDC8+ monocyte numbers, decreased numbers of circulating pDC, impaired B cell organization and function during acute SIV infection associated with BAFF overproduction and deficient T dependent IgA responses.

These studies have led to several publications in excellent journals : as leading or co-leading authors in Blood (n=4), J Exp Med and Immunity, as collaborator in Immunity, PNAS, Blood, FASEB J, Traffic, … The track record of the two PIs who recently joined the team is also very good. In brief, an excellent output.

Assessment of the team's academic reputation and appeal

The team is involved in the LabEX IBEID. It recently attracted 2 PIs with recognized expertise in complementary fields, and a young researcher recently recruited by INSERM. The team coordinator has been involved in the organisation of several international meetings, has been invited at one Gordon conference, and several other international meetings with a broad audience. She was recently awarded the Oudin prize from the French Society of Immunology, and has given many seminars in foreign institutes. Excellent fund raising activity, with several projects supported by ANR, DIM, ANRS, ARC, INSERM-DHOS...

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

Excellent interactions with the socio-economical environment. Indeed the research topics addressed by the team involve immune monitoring of several HIV patient cohorts, and have led to two patents and identification of biomarkers with potential prognostic significance. The team coordinator has contributed to several TV interviews and articles in broad audience non-specialized journals such as Science et Vie. She is a member of several scientific councils, was recently elected president of the Société Française d'Immunologie and the european foundation Acteria, and was the former president of an INSERM evaluation committee. Another PI from the team was also a member of section 24 of CoNRS.

Assessment of the team's organisation and life

No particular comments. Fruitful collaborations have already been established between the team leader and the PIs that recently joined the team.

Assessment of the team's involvement in training through research

Excellent PhD training : 4 PhD theses ongoing, 5 delivered since 2007. Participation to several national / international courses.

Assessment of the five-year plan and strategy

In line with its recent achievements, the team will (i) pursue studies on the characterization of DC subsets which are the best ones for cross presentation, and of the underlying mechanisms of this process, (ii) monitor the BDCA3+ DC equivalents in response towards Ab-fused vaccinal Ag in macaque studies, (iii) assess the mechanisms of crosspresentation of live Ag by DC and its dependence on cell stress, (iv) analyse the role played by type I interferon in immune hyperactivation associated with acute SIV/HIV infection and its impact on subsequent control of opportunistic infections, (v) extend its immunomonitoring studies in HIV1/HIV2-infected patient cohorts and assess in particular the prognostic significance of B cell and BAFF alterations associated with acute SIV infection.

The project, which is quite broad, is a balanced blend of mechanistic basic research and translational studies. Its feasibility looks excellent thanks to the complementary expertise of the tenured researchers and the quality of published and unpublished data supporting each research axis. Moreover funding for most projects is already secured for the coming years.

Conclusion

- Strengths and opportunities:

- Solid expertise in DC biology and HIV/SIV physiopathological studies,

- Excellent output with several contribution in high profile journals,

- Dynamic team recently strengthened by the arrival of tenured researchers with complementary expertise on type I IFN and B cell biology,

- Strong interactions with the socio-economical environment,

- Regular recruitment of postdoctoral fellows,

- Well balanced project integrating basic and translational studies, good feasibility and funding secured.

- Weaknesses and threats:

No real weaknesses. Although well structured, the project addresses many different topics, which might be a pitfall.

- Recommendations:

Focusing on a more limited number of sub-projects could further enhance the international visibility of the team.

Team 26 : Comparative cell biology of host-apicomplex interactions

Name of team leader: Mr Gordon LANGSLEY

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2(1.5)	2(1.5)	2(1.5)
N2: Permanent EPST or EPIC researchers and similar positions	2(1)	2(1.5)	2(1.5)
N3: Other permanent staff (without research duties)	1	1	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1	1
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	6	6	5

Percentage of producers	*100 %*

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	4	
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	3	3

• Detailed assessments

Assessment of scientific quality and outputs

The team is well known in the field of apicomplexan parasites. It is built with one DR1, 1 PU-PH, 1 MCU-PH, another one is leaving, 1 post-doc, 4 phD students and 1 engineer. A CR1 CNRS will join the team in 2013.

The team focuses on apicomplexan parasites: *Theileria* and *Plasmodium*, and their interaction with host cell signaling pathways, especially with the activation of the host cell PKA and JNK kinases. Several interesting issues were revealed, such as evidence that the upregulation of the JNK/AP1 pathway increases the expression of recycling endosome rab11a gene in *Theileria* infection. Similarly in *Plasmodium* infections (included in the MALSIG-FP7 consortium started in 2009), the team found that the biogenesis of the IMC is dependent on vesicular transport from Golgi to IMC by a plasmodial GTPase RAB11B. They have also noted the role of c-AMP dependent PfPKA which regulates the growth of Plasmodium by modulating host cell permeation pathways. Interestingly CK1 and PKA were identified as Rab-effector kinases. A phosphoproteome analysis confirmed the importance of the cAMP-PKA signaling the role of which will be extensively investigated in the future.

In a side project, the metabolism of H2O2 has been shown to impact on the adhesion and motility of *Theileria annulata*-transformed macrophages. TGF-beta dependent invasiveness of infected bovine leukocytosis was epigenetically regulated by MMP-9 through trimethylation of H3K4, catalyzed by the methyltransferase SMID3. This point is important; however it has not generated a subsequent project. Another side-project included in the labEx Parafrap has led to an innovative vaccinal approach against Tropical Theileriosis, based on genetic knockdown of c-Jun, which attenuates *T. annulata*-transformed macrophages. It is an on-going project that will be tested by experimental infection of calves at the Ecole Nationale de Médecine Vétérinaire de Sidi Thabet in Tunisia.

These studies have been published in the best journals in the field. The team has published a total of 51, 33 of which were published with team authors as leading authors (first and/or last author): 24 research papers (Micr Infect, Cancer Res, Proteomic Res, Infect Immun, J Immunol, Plos Pathog (4 times) Mol Biochem Biol, PLos One, IJP, Cell Mic, ...). The clinical parasitology group has produced 23 clinical papers in the field of parasitology and mycology in very good journals such Clin Infect Dis (IF 8,1). Of interest are the papers published by the newly recruited CR1, which include 2 outstanding Blood papers in 2012.

Assessment of the team's academic reputation and appeal

The team is an internationally recognized leader in networks. The PI has set up numerous collaborations, mostly national and very successful, with colleagues from CNRS UMR 7150 and UMR 7216 in the field of cancer. International collaborations have been set-up through the MalSig consortium and the PiroVac program and a recent 2011 ANR grant. The PI, as a leading partner, is dynamic and very successful. He has coordinated the MalSIg consortium and contributed to Pirovac by coordinating a workpackage. He has also coordinated a work package in a COST program action on apicomplexan biology and in a Wellcome Trust funded network on Theileria.

The PI is an eminent and internationally well-known PI. He has been invited at 14 meeting since 2007 and has been chairman in two international meetings. He has contributed to AERES evaluations and was a member of the ANR panel (2011 an 2012). He is also an academic editor of Plos One. The lab participates to the Lab EX program through the ParaFrap network, with the objective to produce attenuated phenotypes of *Theileria annulata*, a major parasitic disease for cattle.

One of the team scientists has organized European Multicolloquium of Parasitology in 2008 in Paris and the French National Toxo Club every two years in Cochin. He is the general secretary of the French Society of Parasitology and is the vice-president of the European Federation of Parasitologists since 2008. He also contributes to the visibility of the team in emerging countries, especially from North Africa and the Middle-East.

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

The team has applied for a patent on synthetic peptides binding to PP2A in 2008.

The PI is the author of a book chapter on Theileria versus cancer in "The immune response to infection" from ASM press.

Assessment of the team's organisation and life

The connections between the physiopathological studies led by the PI and the clinical studies led by one of the team scientists are not obvious and could be strengthened.

Assessment of the team's involvement in training through research

One team member is teaching in master 1 Health and Medicine and in master 2 in Genetics at the Paris Descartes University. The 3 PhD students were in the laboratory between 3 to 5 years. Two scientists are involved in teaching in medical faculty and contribute to be attractive for young medical students. The team organizes a "scientific writing" course for PhD students and post-docs.

Assessment of the five-year plan and strategy

Most of the projects are derived from previous achievements of the PI's on *Theileria* and *Plasmodium*. In addition, with the arrival of a CR1 CNRS, a switch toward malaria is expected, such as a project on RBC adhesion and deformability of the plasma membrane. In general, the overall project will continue to decipher the role of JNK1 versus JNK2 in modulating the glycolytic and pentose pathways. Preliminary data indicate that JNK activation results in an anti-oxydant response by suppressing the transcription of genes coding for essential key aminoacids, slowing down the Krebs/Tricarboxylic acid cycle and ROS generation.

The team will also develop an interesting project at the interface between parasitology and cancer. It will decipher the role of PKA, a cAMP-dependent protein kinase, induced by high levels of TGF-beta and its relation to Ca2+ trafficking. The consequence of its activation will be investigated for cAMP-mediated cytoadherence in malaria RBC adhesion depending on H2O2 levels and plasma membrane deformability. This project is funded by the Bill and Melinda Gates foundation and may lead to a new target to block transmission. This part will be supervised by the new CNRS scientist. MyoA and MTIPm components of the glideosome could be two other targets of PKA at least in a subpopulation involved in Rab11A mediated transport. Alhough the field of kinases in malaria is very competitive, the work on PKA is very innovative.

Several internal "Cochin" collaborations are put in perspective without any precision on budget and feasibility, such as : (i) detection of key redox enzymes, the role of HIF-1alpha activation, the role of CD147/42B and beta arrestin in cAMP regulation and iRBC endothelial adhesion.

Although funding of most projects seems to be secured, a selection of the most interesting projects might be necessary.

The joining of the new CNRS scientist should ensure the continuation of a dynamic Malaria program on innovative projects. There is an outstanding network of collaborative projects and national/international partners.

Conclusion

- Strengths and opportunities:

From the oral presentation, but not from the report, which was not clear enough, the outputs and the subsequent projects as well as the general objective of the unit were well outlined. The theme, identification of novel pathway for the regulation of host cell by apicomplexan parasite, is innovative. The team is reinforced by the arrival of a new CR1 CNRS. This recruitment is crucial and will increase the quality of the on-going projects and the building of new projects on Plasmodium gametocyte sequestration.

The team has made several important contributions in the projects proposed. The publication record is very good.

The team proposes an innovative and coherent project, and all technologies necessary to carry out the projects are available; the introduction of the gametocyte project is a real breakthrough.

The team has obtained a large number of international grants, and recently a grant from the BMG foundation. It is also part of the LabEx ParaFrap. It has a very good participation in European Networks. Financial support is thus significant and largely sufficient.

Collaborations at the national and international levels are outstanding. The presence of one postdoc and 2 PhD is fine and should be sufficient for the achievement of the project.

- Weaknesses and threats:

The team is rather small, and the many projects presented are very ambitious. The attractiveness for the recruitment of novel researchers and technicians is not very strong. Although there is an important activity of clinical research (more clinical papers published than research papers since 2007), there appears to be little connection between the clinical group and the basic research group.

- Recommendations:

The committee recommends an increased integration of the clinical parasitology work with the more basic research that could be achieved, i.e., by integrating the "HU" in the novel on-going project on Malaria.

Team 27 : Regulation of T-cell effector functions: from basic research to cancer

Name of team leader: Mr Bruno LUCAS

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3(1.4)	3(1.4)	3(1.4)
N2: Permanent EPST or EPIC researchers and similar positions	3	3	3
N3: Other permanent staff (without research duties)	3	3	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)			
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	9	9	6

Percentage of producers	*100 %*

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	5	
Theses defended	3	
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	5	5

• Detailed assessments

Assessment of scientific quality and outputs

The team originates from the merging of two teams. It focuses on two main topics dealing on the one hand with the role played by TCR signaling and self reactivity on the shaping of the T cell repertoire, and on the other hand on the analysis of tumor-specific T cell responses and mechanisms of immune escape in a mouse model of spontaneous melanoma induced by the RET oncogene. Studies performed around the first research line have provided new insights into the putative links between lymphopenia-induced T cell proliferation and autoimmunity, the role played by regulatory CD4 T cells in the control of peripheral T cell self reactivity, and the characterization of new surface markers (such as Ly6C) associated with thymocyte self-reactivity. Analysis of antitumor immunity in RET mice have highlighted the key role played by CD8 T cells in the control of tumor spreading, and a quite unexpected contribution of Ly6C+ monocytes to tumor dissemination and vitiligo in this model. In parallel, studies performed in melanoma patients in close collaboration with an oncodermatologist within the team have unveiled enhanced T cell infiltration of cutaneous metastases by dacarbazine.

These studies have led to regular publications in very good specialty journals as leading authors (Blood, 4 J Immunol, Eur J Immunol, J Invest Dermatol, PLoS One). Several collaborative studies, in particular with the team of JPA (Singapore), has been published in even higher profile journals (J Clin Invest, PLoS Biol...). This is a very respectable output.

Assessment of the team's academic reputation and appeal

Two talented young researchers have joined the group, initially as post-docs. Both were recently hired by INSERM and CNRS, respectively. The PIs actively participate to various major national research networks. This underlines the good attractivity of the team and its national reputation. In addition 2 PU-PH play an active role in the team, and contribute to the implementation of translational research programs dealing with immunity against melanoma. The team also has one technician and two engineers. The capacity to raise funds is very good (grants from ARC, LNCC, Fondation de France, ANR, INCa...).

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

The team leader has chaired the committee 24 (Cellular interactions) of CoNRS from 2008 to 2012 and has taken part in many AERES committees since 2008. Some projects show a strong biomedical component. The number of invitations at international meeting seems nevertheless quite limited.

Assessment of the team's organisation and life

The PIs will be deputy director of the III department. Some fruitful collaborations have been established between the two former team leaders, and have resulted in joint publications. The young researchers that recently joined the team will directly contribute to several research axes related to those implemented by the former PIs. This reflects a good team management and appropriate program integration.

Assessment of the team's involvement in training through research

3 PhD theses have been defended since 2007, 2 PhD theses are ongoing. The PI is member of the PhD school council (ED 419).

Assessment of the five-year plan and strategy

The team develops two topics. They recently got evidence that expression of the Ly6C marker could allow distinction of T cell subsets with different affinity for self antigens. The team will determine the transcriptomic profile of these two populations, and will compare the recirculation of these two populations by intravital microscopy. This work will be performed on CD4 T cells Treg cells and CD8 T cells. In addition they will also analyze the biological function of these T cells subsets. This is a quite original project, which clearly benefits from their recognized expertise in the field. It addresses a timely issue, as suggested by recent publications by other teams in high profile journals on a very related topic.

The second project will focus on melanoma, and will assess in the RET melanoma model the relationships between Treg infiltration in derma and the occurrence of melanoma and tumor escape. A particular focus will be given on analysis of Ly6C+ and – Treg cells, and on the links between vitiligo and the frequency of Treg in both the RET model and human melanoma patients. The role played by IL4L1 and NOS2 in the regulation of T cell immune response and myeloid recruitment will be also assessed.

The proposed plan includes several collaboration with several teams with complementary expertise in basic and clinical research, both inside and outside the Cochin institute. This is a very good strategic choice, that has led to excellent publications in the past. The melanoma studies are of potential importance because vitiligo is associated with a good prognosis in melanoma patients. However the biomedical impact of studies done in RET mice is hampered by the yet debated transposability of this model to human melanoma. In this respect, exploitation of BRAF transgenic mice should be encouraged. Finally while analysis of IL4L1 is rather new and interesting, the NOS2 project was felt by the committee as less innovative in a very competitive field.

Conclusion

- Strengths and opportunities:

The interactions with clinicians in the field of melanoma should lead to good fondamental and translational science. In addition the approach to generate IL4L1 RET deficient mice is quite innovative and will lead probably to new and important discoveries. The capacity to use intravital microscopy should help the team implement their studies with very new and up to date approaches. The work on Ly6C Treg may lead to more basic breakthroughs and should benefit from the recognized expertise of the team in the field.

- Weaknesses and threats:

A significant concern is that most parts of the project stem from preliminary and yet unpublished data. The tumor model RET might have some limitations and exploitation of BRAF transgenic mice should be logically foreseen in the coming years.

- Recommendations:

The tumor model RET might have some limitations and exploitation of BRAF transgenic mice should be encouraged.

The study of IL4L1 could be very innovative and could be prioritized over the NOS2 study.

The arrival of one CR1 (merging) and recruitment of one CR1 and one CR2 represent excellent opportunities to strengthen the team, as long as their projects remain close enough to the main focus of the laboratory.

Team 28 : Biology of Phagocytes

Name of team leader: Ms Florence NIEDERGANG

Workforce

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

Percentage of producers	*100 %*

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

• Detailed assessments

Assessment of scientific quality and outputs

The team studies the biology of phagocytosis in macrophages. Although this is a competitive and challenging field, the team proposes focused approaches and has led to a number of significant advances. The scientific output of the team leader is very good by the quality of the research articles that have been published, with 5 research articles published as a last author, in journals such as Blood (2 articles), Dev Cell, J Cell Biol and Mol Biol Cell. The team leader has also published a number of review articles (including in « Traffic » and « Immunobiology »), attesting of the broad view and analyses she provides to her domain of research. The team leader is also associated to research articles through collaborations (articles published in J. Exp. Med., FASEB J, J. Immunol. etc.).

Assessment of the team's academic reputation and appeal

The visibility of the team is very good with one invitation to a Gordon conference, and a good implication in scientific meeting organization (3 national symposia and 2 European meetings). The team has organized 2 symposia (2009 and 2011) since 2007. The team has attracted a number of French trainees (PhD students and post-doctoral fellows), but no international trainees, and in 2011, another PI (DR2 CNRS) has joined the group. The team leader has been invited to several national and international conferences. The team members are member of several French Societies and two European Societies. No participation to European projects or networks is reported. Strong collaborations within the institute Cochin are mentioned, as well as national collaborations, 3 international collaborators are identified. The team has obtained several national grants (Ville de Paris, ARC, ANRS, ANR, etc), but no international grant.

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

The team leader is highly implicated, on a voluntary basis, in teaching (>100h per year of teaching). She has also participated to evaluation committees (AERES committee and a grant review committee, and more recently in the CoNRS section 27).

No patent has been filed. No contract research or collaboration with industrial partners is reported. No collaboration or contacts with clinicians, medical units or patient association have been identified.

Assessment of the team's organisation and life

The team leader has secured a good amount of funds, through competitive research funds calls (ANR for instance), thereby warranting the material functions of the team, and salaries for non-permanent personnel. The team is entirely organized around the team leader. Although a CNRS DR2 has joined the team in 2011, the implication of this investigator to the team's life and his contribution is not exposed clearly.

Assessment of the team's involvement in training through research

Four PhD students have been trained within the team over the evaluated period, which is a very strong record for only one PI. Three post-doctoral fellows have also been trained within the team. The team leader is heavily implicated in teaching and particularly in Master programs. The students in the team have published a number of first-authored research articles, and have obtained prizes, which constitutes a positive sign for the quality of the training environment within this team. No contribution to international training networks or summer schools is reported.

Assessment of the five-year plan and strategy

Overall, 3 main themes of research are proposed. Those 3 themes are complementary, original and supported by strong expertise within the team :

(i) Molecular signaling and phagocytosis- Strong expertise by the team head that could nicely be completed by the other PI,

(ii) Perturbation of macrophage function by HIV infection- Very original approach where the team leader has established herself as an expert and that is well supported by important publications in the domain,

(iii) Regurgitation of dendritic cells- Very successful program, extremely original, where the team head can be considered as a leader.

The three scientific themes proposed are original and ambitious, well supported by funds that have been obtained in each domain. From that point of view, this supports the feasibility of the five-year project. Trainees have been identified to work on each project, but it is not clear how these projects will position the other PI of the team, and what will be his overall contribution to the general research plan. This poses the problem of the feasibility of the research plan in terms of study supervision, especially if one considers the future involvement of the team leader as a deputy director of the department, as well as other responsibilities.

Conclusion

- Strengths and opportunities:

A major strength comes from the fact that the team leader is visible, having published in each domain of research that are proposed and she has also secured all the funds necessary to each of the projects. The publication record is excellent, and all technologies necessary to carry out the projects are available and mastered at the Institute. The collaborations are carefully chosen. This overall research proposed should strengthen the position of the team leader on the national and international scene. Another important strength is the quality of the research training provided by the team leader. Finally, a new post-doctoral fellow will be presented for a permanent position to increase the critical mass of the team.

- Weaknesses and threats:

The team leader is supposed to take on new functions as deputy director of the department of immunology, which is the largest department of the institute, composed of several hundreds of persons. In addition, she has a strong commitment to teaching, but it must be pointed that she has already stepped down from part of her teaching. The work overload of the team leader has to be considered as a threat and is not compensated by a clear plan and participation of the new research member (DR2 CNRS) joining the team. The contribution of this researcher is not fostered at its most. Finally, the connection between the three projects is not evident.

No translational approaches or attempts, even through collaborations are proposed. The research proposed does not present translational vision and applicability of the research.

No technical permanent position is attributed to the team. Such a position would strongly relieve the team leader from several aspects of technical training and day-to-day supervision.

- Recommendations:

Recommendation could be made to the team leader to focus her research projects on one or two themes, considering her workload and her present and future commitments. It is impossible to specifically recommend dropping one or the other project, as they are all funded and quite successful. Alternatively, she might want to clarify and foster the implication of the joining DR2 on several aspects of the research project. Attracting new young investigators to the team will also be an important asset.

Efforts on technology transfer would also strengthen the position and visibility of the team.

The expertise within the team would also need to be supported by a permanent position of technician or research assistant. Finally, it is recommended to increase its international exposure and visibility, notably by participating to ambitious international programs, including European Networks.

Team 29 : Retroviruses, quiescence and proliferation

Name of team leader: Ms Claudine PIQUE and Ms Florence MARGOTTIN

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2	2	2
N2: Permanent EPST or EPIC researchers and similar positions	2	2	2
N3: Other permanent staff (without research duties)	1	1	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2	2
N6: Other contractual staff (without research duties)	2	1	
TOTAL N1 to N6	9	8	6

Percentage of producers	*100 %*

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2	
Theses defended	7	
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	3

• Detailed assessments

Assessment of scientific quality and outputs

The team implements three main lines of research :

(i) HIV and infection restriction mechanisms : of particularly note is the elucidation of the probable major mechanism of SAMHD1 antiviral action in macrophages. The finding that SAMHD1 depletes dNTPs is elegant and simple, and was published well in the face of substantial international competition.

(ii) HTLV research : The neuropilin-HTLV receptor story has evolved well and the combined use of the different receptors in virus entry was investigated. This research seems not to be proposed anymore as a priority.

(iii) Other work into the function of HIV-1 and HTLV regulatory and accessory proteins is interesting and maintains a strong momentum of novel research in the group. Finally, the continuing analysis of ubiquitination and SUMOYlation of viral regulatory proteins provides a healthy continuum of strong research papers.

Publications. The two teams have published well over the past period. Clearly the star paper is the SAMHD1 mechanism in Nature Immunology, but several Blood, Plos Pathogens and JBC papers add impact. Finally, several papers in more specialized but highly respectable journals (JVI, Retrovirology) mean that these groups have a balanced but impressive portfolio of publications that reveal a robust and continuing contribution to the field.

In summary the output grade is excellent with some very strong papers in high-impact journals, several strong papers in specialized journals.

Assessment of the team's academic reputation and appeal

Visibility grade Strong international presence in the international community is emerging. Investment in travel to international meetings would help with a higher profile, networking and future invitations to present.

Funding. The team is well funded and there is no reason why this should not continue.

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

Good interactions with the public for dissemination of understanding of science.

Assessment of the team's organisation and life

Noparticular comments. The added value of the two CR1, who have not published that much during the last 5 years is not obvious.

Assessment of the team's involvement in training through research

7 PhD theses completed, 2 more in progress. 2 M1 and 7 M2 students trained.

Assessment of the five-year plan and strategy

Most fruitful lines of research dealing with HIV and HTLV regulatory and accessory proteins will be logically pursued. New synergies are anticipated from the merging of these two topics.

Conclusion

- Strengths and opportunities:

The two groups individually show an energetic approach to research that will no doubt be enhanced by the recent merger. Combining expertise and manpower ought to allow synergy that will deliver in-depth answers to the proposed research questions. The level of originality is high, in particular for the work conducted on SAMHD1, with several new discoveries being claimed by these two groups over the past 5 years in the face of strong international competition.

- Weaknesses and threats:

The research portfolios of the two groups are relatively broad, and their combination means that there is now a substantial breadth of interests. Although this is not in itself a weakness, the group leaders may have to make some decisions on which areas may need to be prioritized in order for the team to focus on the major questions that evolve from current studies. This prioritization may be focused around synergistic projects shared between the two groups that would give objective evidence for synergy between the two PIs.

Two CR1 scientists joined the team in 2007/2008. Their contribution to the scientific work is so far quite limited.

- Recommendations:

To consider in more detail the future plans for the newly merged teams and to attempt to prioritize projects so as to address the questions of the highest impact with the greatest resources. To demonstrate true synergy between groups by co-publication or other robust measures of collaboration. The project “SAMHD1 – restricts HTLV1” set up in collaboration by the two teams will certainly contribute to achieve this aim.

To consider entry into the area of HIV-1 latency and ‘functional cure’ as this group may have a lot to contribute to this area of research.

The team should pay attention to encourage the two “Chargé de Recherche” to increase their scientific responsibility, get fully involved as project leaders and contribute to the financing of the research.

Team 30 : Barriers and pathogens

Name of team leader: Ms Isabelle TARDIEUX and Ms Claire POYART

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3(2.5)	3(2.5)	3(2.5)
N2: Permanent EPST or EPIC researchers and similar positions	3(1.3)	3(1.3)	3(1.3)
N3: Other permanent staff (without research duties)	3	3	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2	2
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	11	11	8

Percentage of producers	*100 %*

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

• Detailed assessments

Assessment of scientific quality and outputs

Among the main achievements of the team can be mentioned the following results :

Project #1. Progress has been made in the understanding of the tight junction between Plasmodium zoites and the host cell. This has led to the identification of a host cell F-actin ring during parasite entry, recruitment of Arp2/3 and cortactin. The role of the parasite proteins AMA1 and RON2 for the structure of the tight junction has been refined (by constructing conditional knock-down zoites). The team has previously identified toxofilin as an actin-binding protein and has now solved the 3D structure of the toxofilin-actin complex. It has also clarified the role of toxofilin in invasion (impairment of cortical actin disassembly).

Project #2. The team is in charge of the National Reference Center for streptococci and liaises with a network of > 280 clinical microbiology laboratories. It analyses approximately 500 GBS (Group B Stretococcus) strains/year and has identified a capsular serotype III (ST-17) as a hypervirulent clone. The team has identified HvgA as a specific protein in ST-17, established its role as an adhesin in GBS meningitis, in intestinal colonization and in translocation of intestinal barrier and Blood brain barrier (BBB). The team has re-examined the FASII system as drug target in GBS and *S. aureus* (published in Nature). It has characterized the two-component system CovSR, identified the membrane protein Abx1 as essential for CovSR regulation by binding to CovS and Stk1. It has examined the role of PerR in peroxide stress response and identified members of the PerR regulon. These are all major contributions to the field.

Publications : since 2007, between 3 and 9 publications/year (total of 51 intl. reviewed papers, 26 of which in leading positions, first and/or last author). Most papers in microbiology and parasitology, one in Nature, 2 in PNAS, 2 in Host Cell Microbes, one in J. Exp. Med. and one in FASEB J. This is an impressive output.

Assessment of the team's academic reputation and appeal

The team is part of a LabEx, Idex Sorbonne Paris Cité, and the LabEx Parafrap. It has established many collaborations in France (INRA, I. Pasteur, Grenoble …) and in foreign countries (Sweden, Austria, Israel, Scotland, US), participates to 3 ANR projects and coordinates two ANR projects (APIINVASION & HyperVir GBS), participates in a FP7 consortium (ERANET). The team has taken part in several national and international meeting organizations, the team leader is editor of 3 microbiology journals (including Editor-in-Chief for Microbiology), member of several national and 2 international advisory boards and committees. Several invitations as speakers. The team leader was recently awarded an FRM prize "Jacques Piraud" in 2010.

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

Patent application for the detection of CC17 GBS (2005), translational research funded by APHP, Institut Mérieux and IRT biopôle Lyon. The team addresses several topics that correspond to major health issues, and thus could have a major biomedical impact.

Assessment of the team's organisation and life

No particular concerns. At first sight, the team corresponds to the merging of two very distinct projects undertaken by two well recognized and independent researchers. Therefore the team could be split without affecting the quality and feasibility of each project. Although there are no joint publications, the two PIs seem to implement in a coordinated fashion technological developments that are useful for their respective programs.

Assessment of the team's involvement in training through research

The team supervised 2 secondary school students in 2011 and 2012, a secondary school class (2008/9 and 2009/10). It currently trains 2 PhD students, 3 PhD theses were successfully defended. The team is also involved in teaching at the Medical Faculty, at I. Pasteur and ENS Cachan.

Assessment of the five-year plan and strategy

The two groups have decided to merge and work together on the mechanism of BBB, either by GBS or by *T. gondii*. The rationale is well presented (one pathogen causes strong inflammation in the brain and meningitis, whereas the other causes essentially a silent CNS infection). Mouse models, and ex vivo models, together with microfluidic devices, will be used, in conjunction with high resolution imaging. The first objectives are in vitro and ex vivo explorations of the BBB crossing, which hopefully will identify some of the key steps in this process. The third objective aims at studying this process in vivo, using appropriate mouse models, including mice deficient for various components. Finally, the 4th objective aims at identifying the microbial and host molecules involved. All technologies and infrastructures for this project are in place or will be available soon. In particular the project will benefit from the LabEx for novel tools.

The second project concerns a new pathogen, GAS (Group A Stretococcus). In this project the bacterial factors for colonization of the female genital tract and dissemination, as well as the host factors will be identified. The first objective will make use of high throughput sequencing of various GAS strains isolated from different patients and transcriptomic profiles of the GAS grown in different culture conditions. This will hopefully lead to some virulence factor candidates. These candidates will then be evaluated by classical approaches, such as gene KO and infection experiments. The second objective will make use of approaches developed in the first project. Altogether, these are all exciting projects, although it is not obvious how they may link together (except that they deal with Streptococci).

Conclusion

- Strengths and opportunities:

The strengths clearly reside in the expertise of the main investigators on barrier crossing by GBS and *T. gondii*.

The project will also make use of important infrastructures and imaging technologies available at the Cochin Institute, and developments expected from the LabEx, as well as from numerous well-chosen collaborations. Some of these collaborations have proven their effectiveness (e. g. I. Pasteur).

An important asset is also the Centre Ntl. Ref. on Streptococci, which allows to directly link basic observations with "real life" and provides access to important strain collections. The team makes good use of this asset.

The leaders of the group have an excellent publication record. Financial resources also appear to be secured.

- Weaknesses and threats:

The group is rather small (2 ½ senior scientist FTE), and it may be problematic to develop projects on three pathogens in parallel at an internationally competitive level, although the team has shown in the past that they are internationally competitive. There has been some tendency for a lack of focus in the past, and both groups that now make up this team have to learn how to strengthen internal collaborations.

- Recommendations:

Given the ambition of the project, it is important to keep focusing. The group is quite small and it may be difficult to work on three different pathogens in a competitive manner. Also, make sure that the group is properly managed with real collaborations between the team leaders, for example by exploring the BBB trafficking of GBS by the Toxoplama group. This is not yet visible from the publication list.

Team 31 : Neutrophils and Vasculitis

Name of team leader: Ms Véronique WITKO-SARSAT and Mr Luc MOUTHON

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3(1.6)	2(1.5)	2
N2: Permanent EPST or EPIC researchers and similar positions	1	4(0.4)	4
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.)	2	2	2
N6: Other contractual staff (without research duties)	1	1	
TOTAL N1 to N6	9	11	8

Percentage of producers	*100 %*

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	9	
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	2

• Detailed assessments

Assessment of scientific quality and outputs

This well recognized team in the field of vasculitis and neutrophil biology is co-headed by a director of research and a medical professor, and also includes several clinicians. Several original observations have been made during the last 5 years, regarding (i) a new anti-apoptotic function played by PCNA in neutrophils, (ii) the direct contribution of PR3 to autoimmune processes associated with GPA (Granulomatosis with PolyAngiitis) and (iii) the characterization of target antigens for self-reactive Ag associated with Giant Cell Arteritis.

These observations have led to an impressive number of basic and clinical publications in excellent specialty journals. The impact of these publications is remarkable, as exemplified by a sustained pace of publications in high impact journals : J. Exp Med (2010), Blood (2007, 2010) J Biol. Chem. (2012), J. Immunol. (2009, 2012), Ann Rheum Dis (2012), among others. Members of the team are also considered as opinion leaders in their field and this is attested by a number of reviews they have published (Nat Rev Rheumatol., FEBS J, J. Innate Immun, etc.). From the reported period, one of the team leaders has published more than 40 original articles from clinical studies and is a co-author on more than 60 other ones.

Assessment of the team's academic reputation and appeal

The visibility of the team is excellent. Both investigators have an international visibility in their domain. They are invited on a regular basis at international conferences and prestigious institutions to give lectures or to chair scientific sessions in the domain of vasculitis, autoimmunity and neutrophils. For instance, one of the co-PIs has been invited to give lectures at the World Congress on Scleroderma, at the International Congress on Autoimmunity, at the Asian Congress of Autoimmunity, etc. The other co-PI has been invited to give lectures at the "Neutrophil in Immunity Conference" in Canada, at several workshops on ANCA (in the US, in Sweden), on Phagocytes and neutrophils (in Greece, in Germany), etc.

Both team leaders have organized a number of scientific meetings (the world Congress of Inflammation, the world congress on Scleroderma, as a couple of examples).

Both investigators are members of editorial boards of a number of journals.

They are also part of a number of national and international networks (Labex, European Phagocytic group, etc.).

The team has obtained funds from national granting agencies (ANR, PHRC, VLM), from pharmaceutical partners, but also international competition: 2 European projects: NEUPROCF, and EULAR.

Their reputation and visibility are on all counts excellent.

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

Both team leaders are heavily involved in patient associations and social networks. VWS has attended a number of meetings organized by patient associations (Fondation Vaincre la Mucovicidose, the Arthritis Foundation), and has participated to the "Virades de l'Espoir". LM has also participated to the annual meeting of the French Association of Scleroderma patients, organizing information sessions to patients.

Both team leaders have strong interactions with industrial partners, through research contracts on neutrophils and vasculitis, on PCNA and leukemia (for VWS), and on biomarkers of systemic vasculitis (for LM).

Finally, both team leaders have imposed around their research, strong directions towards biomedical and technology transfer. Two international patents have been filed by one of the co-PIs and 3 national patents have been filled by the other one.

Here again, the performance of this team in building interactions with the social and economic environment is excellent on all counts.

Assessment of the team's organisation and life

The structure and function of the present team could serve as a role model for successful interactions and exchanges between basic science and clinical research. The two PIs have put together a highly successful way to interact and to build their projects from information obtained in the clinic towards basic science questions and vice-versa. The synergy between basic and clinical research is very strong, feeding each other in a most efficient way. As a matter of fact, the two PIs are publishing successfully together (8 joint publications).

Research funds have been secured by all partners to insure the material functions of the team, salaries for non-permanent staff have also been secured.

The strategy for development of the team has been identified: the possibility for a young basic scientist coming back from a post-doctoral period in the UK to be recruited to the team is proposed. Vibrant scientific animation has been put together on a very regular basis, including research-in-progress reports and journal clubs.

Assessment of the team's involvement in training through research

Since 2007, a number of master students (both M1 and M2), but also 9 PhD thesis have been successfully defended within the team, while 4 PhD thesis are still in progress. The PhD students that have been trained within the team have published a number of first author research articles, some of them have obtained prizes, which together constitutes a very positive sign for the quality of the training environment within this team. Both PIs are implicated in teaching : Master courses on inflammation within the Labex Inflamex educational task for LM, Master 1, DU and DESC courses for VWS.

Assessment of the five-year plan and strategy

The 3 research themes proposed by the team are logical, well organized, well supported by the strong expertise within the team and funds have been attracted to support them.

Cytoplasmic PCNA scaffold in the control of neutrophil apoptosis and inflammation. This is an original scientific theme, and the team has a strong expertise to conduct the project. It has both a basic science and a clinical input, which is a considerable strength.

Pathophysiological role of PR3 in ANCA-associated vasculitis. The expertise and international recognition of the team are very strong for this theme. The project is original and should lead to major advances in the field.

Vascular remodeling and autoimmune vascular disease. Strong clinical relevance is associated with this project, and a strong rationale supports this theme.

Overall, the strategy of this team is excellent, they have elaborated very focused projects, with high feasibility. Their program is novel and ambitious. This team is a model for successful synergy and integration of pathophysiological and clinical aspects.

Conclusion

- Strengths and opportunities:

A major strength comes from the association between the research of the two co-PIs, which has proven to be highly successful and complementary. The team is composed of basic scientists and clinical researchers that optimally interact together. From this strong synergy have emerged excellent scientific outputs, with a number of research articles published in high impact factor journals and a number of patents and collaboration with industry. Each PI is very successful in his field and well recognized individually by their scientific community, but they have also demonstrated their capacity of interacting together for the benefit of new scientific knowledge. By the synergy they have demonstrated, they are placing their team in a unique position in the field of vasculitis and neutrophil biology. They cover both the endothelial and the neutrophil side, and have thus unique ways to investigate those interactions.

The translational spirit of their position as a team has also led to strong technology transfer activities, which is also a major strength, in terms of the team's visibility and financial support.

Finally, they have built up biological collections of serum, plasma, cells (neutrophils, fibroblasts, smooth muscle cells, etc.) from healthy subjects and patients with vasculitis. This constitutes another important strength, first to feed the needs of the basic science experiments, but also, the needs for genetic studies, and finally places the team as an essential and resourceful group on the international scene.

- Weaknesses and threats:

The composition of the team could be fostered on the basic science side for permanent positions: the clinical research side being stronger than the basic research side in terms of the number of people involved. Although already very successful and strong, the basic science research would benefit from additional permanent positions.

- Recommendations:

Although the critical mass is already strong and productive, recommendation could be made to secure a permanent position for at least one additional basic scientist within the team.

5 ● Conduct of the visit

Visit dates:

Start: January 15, 2013 at 8 am

End: January 17, 2013 at 3 pm

Visit site(s):

Institution: Institut Cochin

Address: 22 rue Méchain, 75014 Paris

Second site

Institution: Institut Cochin

Address: rue du faubourg Saint-Jacques, 75014 Paris

Conduct or programme of visit:

Day one – January 15, 2013	
8:00	Welcome : *the AERES scientific delegate and the evaluation committee*
8:45	**Presentation of the Cochin Institute:** activity report and project
	Director of the Institute: Mr Pierre-Olivier COURAUD
9:30	**Presentation of the facilities**
	Heads: G BISMUTH & C PIQUE (candidate Head)
10:45	*Coffee break*
10:45	**Presentation of the scientific departments**
	Head of EMD Department: S VAULONT
	Head of DRC Department: M PONTOGLIO
	Head of 3I Department: A HOSMALIN
12:15	*Lunch*

Split of the committee in 3 sub-committees

Sub-committee 1: Endocrinology, Metabolism and Diabetes

13:15	**Team E1** *F. BOUILLAUD* - Mitochondria bioenergetics, metabolism and signaling
14:30	**Team E3** *R. JOCKERS* **-** Pharmacology and Pathophysiology of Membrane Receptors
15:15	**Team E5** *S. MARULLO* - Receptor signalling and molecular scaffolds
16:00	*Coffee break*
16:15	**Team E2** *J. BERTHERAT* - Genomics and Signaling of Endocrine Tumors
17:30	*Debriefing*

Sub-committee 2: Reproduction, Development and Cancer

13:15	**Team E15** *C. PERRET* - Oncogenesis of digestive epithelia
14:30	**Team E12** *C. DESDOUETS* **-** Cell Cycle and Liver Pathophysiology Receptors
15:15	**Team E10** *B. CHAZAUD* - Stem cell environment and skeletal muscle homeostasis
16:0	*Coffee break*
16:15	**Team E14** *P. MAYEUX & D. BOUSCARY* - Study of normal and pathological hematopoiesis
17:30	*Debriefing*

Sub-committee 3: Infection, Immunity and Inflammation

13:15	**Team E27** *B. LUCAS* - Regulation of T-cell effector functions: from basic research to anti-tumor responses
14:30	**Team E31** *V. WITKO-SARSAT & L. MOUTHON* **-** Neutrophils and vasculitis
15:15	**Team E23** *JD CHICHE* - Stem cell environment and skeletal muscle homeostasis
16:00	*Coffee break*
16:15	**Team E24** *E. DONNADIEU & C. RANDRIAMAMPITA* - T cell interactions: from synapse to cancer
17:30	**Team E28** *F. NIEDERGANG* **-** Biology of Phagocytes
18:15	*Debriefing*

Day two - January 16, 2013

Sub-committee 1: Endocrinology, Metabolism and Diabetes

10:15	**Team E8** *S. VAULONT & B. VIOLLET* - Genes, Nurients and Iron
11:30	*Coffee break*
11:45	**Team E6** *C. POSTIC* - Insulin signaling, glucose sensing and glucotoxicity
13:00	*Lunch*
14:00	**Team E4** *A. LEHUEN & R. MALLONE* - Immunology of Diabetes
15:15	**Team E7** *R. SCHARFMANN* - Control of pancreatic endocrine cell development
16:30	*Debriefing*

Sub-committee 2: Reproduction, Development and Cancer

09:30	**Team E13** *P. MAIRE & N. SOTIROPOULOS* - Genetics, development and pathophysiology of skeletal muscle.
10:45	**Team E16** *M. PONTOGLIO* - Gene Expression, Development and Disease
11:30	*Coffee break*
11:45	**Team E11** *J. CHELLY* - Genetics and Pathophysiology of Intellectual Disability and Neurodevelopmental disorders
13:00	*Lunch*
14:05	**Team E17** *D. VAIMAN* - Genomics, Epigenetics and Pathophysiology of Reproduction
15:15	**Team E9** *F. BATTEUX* - Oxidative stress, cell proliferation and inflammation
16:30	*Debriefing*

Sub-committee 3: Infection, Immunity and Inflammation	
08:00	**Team E18** *S. BENICHOU* - Virus and Intracellular Trafficking
08:45	**Team E19** *C. BERLIOZ & S. EMILIANI* - Host-Virus Interactions
10:00	**Team E29** *C. PIQUE & F. MARGOTTIN* - Rétrovirus, Quiescence and Proliferation
11:15	*Coffee break*
11:30	**Team E20** *M. BOMSEL* - Mucosal enry of HIV and mucoal immunity
12:15	**Team E22** *R. CHEYNIER* - Cytokines and viral infections
13:00	*Lunch*
14:00	**Team E25** *A. HOSMALIN* - Dendritic cell physiology
15:15	**Team E30** *C. POYART & I. TARDIEU* - Barriers and Pathogens
16:00	**Team E26** *G. LANGSLEY* - Comparative Cell Biology of Apicomplexa Parasites
16:45	**Team E21** *S. BOURDOULOUS* - Vascular cell biology in infection, inflammation and cancer
17:30	*Debriefing*

Day three – January 17, 2013	
09:00	**Parallel meetings with representatives of:** - research assistants: *engineers, technicians, admin. staff* - staff scientists: *researchers, clinicians-researchers* - non permanent scientists: *post-docs* - PhD and Master students
09:45	**Discussion with the Institutions representatives**
10:45	**Plenary meeting of the evaluation committee**
13:00	**Discussion with the board of Directors**
13:45	**Plenary meeting of the evaluation committee**
15:00	*End of the visit*

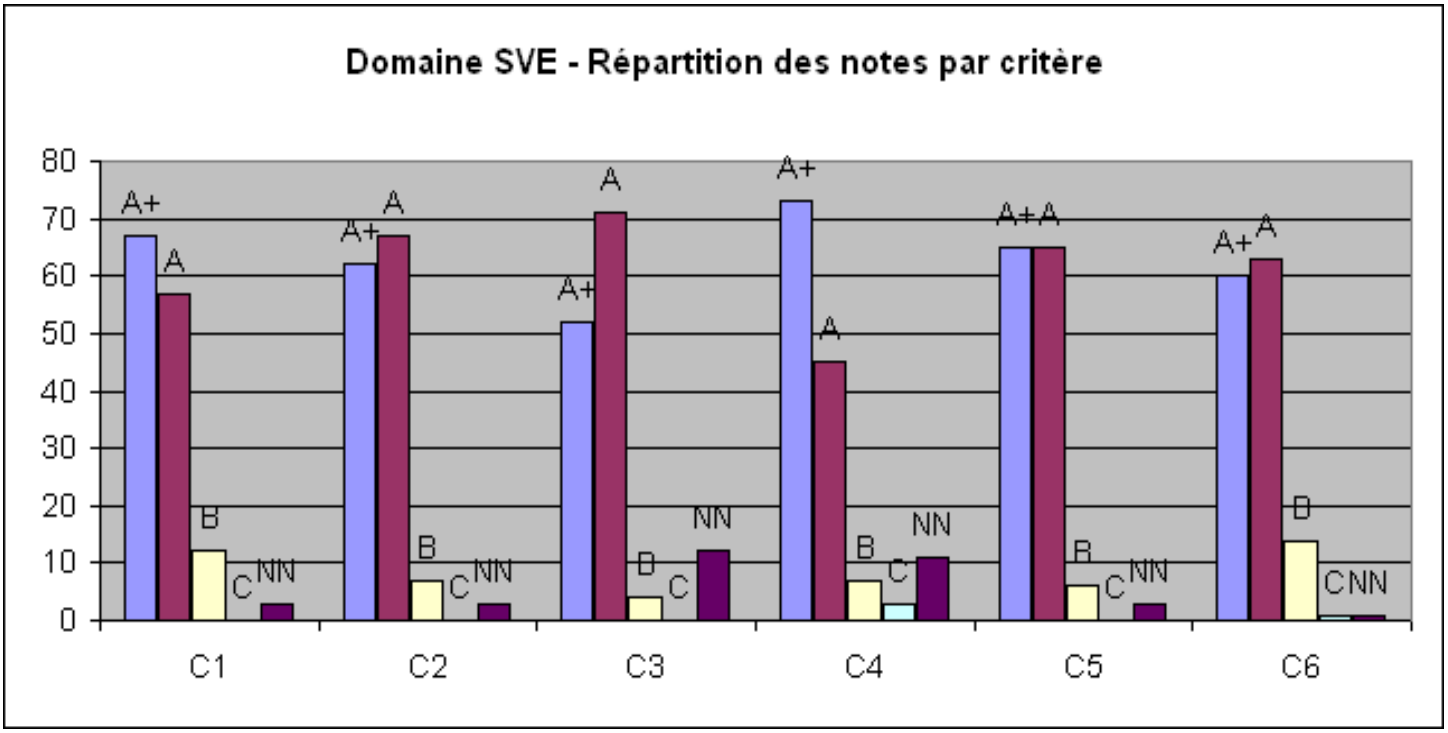
6 • Statistiques par domaine : SVE au 10/06/2013

Notes

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

Pourcentages

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



7 • Supervising bodies' general comments

UNIVERSITÉ PARIS DESCARTES

Vice Président du Conseil Scientifique

Paris le 24.04.2013

Vos ref : S2PUR140006268 – Centre de Recherche Institut Cochin – 0751721N

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

Monsieur le Directeur

Je vous adresse mes remerciements pour la qualité du rapport d'évaluation fourni à l'issue de la visite du comité d'expertise concernant l'unité « Centre de Recherche Institut Cochin »

Vous trouverez ci-joint les réponses du Directeur de l'Institut, Pierre-Olivier COURAUD, auxquelles le Président et moi-même n'avons aucune remarque particulière à apporter.

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

Le Vice Président du Conseil Scientifique

Stefano Marullo, DM, DesSci

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

institut cochin
CENTRE DE RECHERCHE

Pierre-Olivier Couraud
Directeur

Paris, April 23, 2013

We were glad to read that the AERES Committee was very favorably impressed by several aspects of the scientific activity performed at the Cochin Institute, notably by

- the global significant implementation of the quality of research performed in the Cochin Institute, attested by the increased productivity, the significant higher number of research grants and the high proportion of teams involved in the programs of excellence initiative,
- the improved and strong interactions with the hospital and translational efficiency: interestingly, these two items were previously pointed (at the previous renewal evaluations of the Institute) as rather weak, with recommendations to improve them. Obviously, the Cochin Institute has been very successful in addressing these points,
- the quality of the core facilities, one recognized strength of the Institute,
- the support to emerging collaborative projects provided by internal calls for proposals,
- the attractiveness of the Institute for Master and PhD students,
- the observation that « everybody in the Institute is satisfied by the management of the Institute and happy to work at the Cochin Institute with a fairly good *Institute spirit* ».

Regarding the present recommendations of the AERES Committee, here is a point-by-point reply:

1. *Based on the great research potential and quality of the Institute the committee considers that the numbers of ERC applicants and awardees is too low. The committee strongly recommends to the direction of the Cochin Institute to have a much more willful policy to incite several young scientists and team leaders to apply to ERC grants.*

   Regarding the two on-going applications, one has been pre-selected for the second step of the selection process, the other one is still pending. The direction has already encouraged additional applications. In addition, as stipulated in the Project presented to the Committee, an international call for applications will be launched before the end of this year, to recruit top-level, internationally recognized young scientists who will be ERC awardees or will apply to.

2. *The committee considers that the Cochin Institute as a whole lacks major international impact. The committee recommends that the Cochin Institute creates some international scientific events like an annual colloquium and/or summer schools.*

   Because the Cochin Institute was created only 10 years ago, it is quite understandable that its international impact is not yet at the level of a few well-

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established French Institutions. We believe though that the significant implementation of the quality of research, together with the identification of a limited number of major research axes (corresponding to the 3 scientific departments), will contribute to increase the visibility and recognition of the Institute internationally.

3. *The committee is wondering whether the internal translation office, which is managed by a single person, will be sufficient to manage an increasing demand*

Considering that the Committee mentioned "the strong translational efficiency" as a strength of the Institute, we take this recommendation as an encouragement to proceed further in the way the direction of the Institute has been working on since 2008. We are currently working in close collaboration with the newly founded SATT IdF-INNOV: this collaboration will be maintained and strengthened appropriately along the development of the SATT.

4. *The committee strongly recommends to the Direction of the Cochin Institute to incite some teams to develop more integrated projects for a better visibility of the concerned teams*

The Direction of the Institute has been driving in-depth discussions with the group leaders during the past term, that contributed to identify a limited number of complementary research themes; when appropriate, these discussions will be maintained, with the input of the Scientific Advisory Board of the Institute, to clarify or further implement the internal synergy between the project leaders in some teams.

5. *The committee strongly recommends that the ERC as well as the further ATIPE/Avenir grants give rise to independent teams whose activity should be evaluated not earlier than 5 years after their creation*

The direction of the Cochin Institute strongly supports the creation of emerging groups: - the present ERC group was allocated more than 50m² lab space and is financially and scientifically autonomous: in line with the recommendation of the Committee, this group will be proposed as an independent team, affiliated to the EMD department of the Cochin Institute; - a 2012 ATIPE/Avenir group has recently been created as an independent team of the Institute (not submitted to evaluation by the Committee), as a member of the 3I Department. Besides, regarding additional ATIPE/Avenir groups, the decision to propose them as independent teams or autonomous groups will be made on a case-by-case basis.

6. *The committee considers that the Institute should have a willful policy for creating emerging groups from young talented scientists. The committee considers the Cochin Institute should have a long-term plan for its future development through the recruitment of young talented group leaders. The Institute should be careful about keeping some turnover and be vigilant about uncontrolled internal growth of the teams. Clearly some strong factors supporting attractiveness like laboratory space, human resources, dedicated funding, should be the immediate matter of planning to ensure the future development of the Institute*

To support the international call for applications to be launched before the end of this year (see point 1), the Institute will devote resources on its 2014 budget to facilitate the installation of this or these new team(s) in currently available lab

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space (more than 100m² in the Faculty Building). In addition, further support by the Institutions (INSERM, CNRS, Paris Descartes University) will be required, in particular in terms of human resources and dedicated funding.

Regarding the turnover in the Cochin Institute, it was mentioned in our written document that 7 teams present in the Institute since 2010 do not candidate for the next 2014-2018 term (5 teams leaving the Institute, 2 joining another team in the Institute), whereas 3 internationally recognized teams recently joined the scientific project of the Institute, in addition to 3 other teams which joined the Institute since 2010. We believe that this level of turnover (about 20%) is actually very high and reflects the strong attractiveness of the Institute as well as the determination of the direction to ensure the development of the Institute.

We are glad that "the committee is confident that the Director is aware of this issue and has some prospects in that sense » (p11).

7. *The committee strongly recommends that the Cochin Institute makes deep investments in animal housing in order not to hamper many ongoing competitive projects in the teams, and for the Institute to preserve its leading edge activity in the field of mouse experimental genetics*

As presented to the Committee during the on-site visit, the direction of the Institute has been actively working on the implementation of the animal facilities for several months.

- we are in the process of creating a new pathogen-free animal facility, thanks to an important funding obtained from the Région Ile-de-France and INSERM (2.7M€) in 2012. Work is in progress and should be completed early 2014
- we plan to remodel the conventional animal facility in 2013: technical studies and budget evaluation are on-going. A specific grant from Paris Descartes University (200-300 k€) is expected.

Pierre-Olivier Couraud

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Department EMD Team 2

Answers to the evaluation report (Citations of the evaluation report are in italic and quoted between « »)

1-« This team is the result of a recent merging among 3 prior teams »
Indeed our team was finally formed in 07/2011, hence less than a year before the scientific report was prepared. We would like to stress that some of the criticisms raised in the evaluation report have to be considered with regard to this past story.

2- « Based on the expertise of the team more high impact publications would be expected. »
« The team has too many project leaders and as a consequence the number of high impact factor articles is somewhat low ».

The past activities of the three independent smaller groups had to be assembled in the 2007-2012 report. This remark thus considers the result of the past activities of these three groups with regard to the present arrangement into a larger team with extended expertise.

On the other hand this remark is consistent with the purpose of our merging that was to bring together complementary expertise and to increase manpower in order to sustain more ambitious projects with subsequent higher impact.

3- « ...they need to mature their way to better address and solve relevant questions. »

Our merging was not born from addition to a dominating project but from our shared interest about the pathophysiological consequences of modulations/alterations of mitochondrial bioenergetics. This relationship is in fact the unifying project of the team that is realized through the use of different models. The group will have to progressively focus on fewer projects/models taking into account the relevance of the issue, but also its financial support and feasibility. The fact that convergence is under way has been acknowledged by the evaluation committee : « *This has started already as several new projects are led by two senior researchers and should be pursued in order to focus on a limited number of selected and related topics. ».* The evaluation committee also showed its understanding of the benefits of the merging: *« Considering the expertise of the leaders in mitochondrial biology and the relevance of mitochondrial dysfunction in human pathology, it is clear that this team has a great potential… »*

4- « They appear less attractive for recruitment of young scientists since there are no post-docs in the team. » « Recommendations : ... to attract more PhD students and postodcotoral fellows »

Two post docs were present during the 2007-2012 period, the last one left in 12/2011 after three years in the group resident in the Cochin Institute. The two incoming groups restrained their applications for post-doctoral grant and PhDs before the completion of their move to Cochin Institute in order to avoid exposing young fellows to the complications of the moving.

The situation will improve significantly with the arrival of two post-doc fellows in the team: one granted by a FRM fellowship will start on May 2013 for a two years project. The second granted by Paris V University (PRES) will arrive within few months to foster our collaboration with chemists. A third post-doctoral grant application, initiated by a Canadian fellow, is currently under evaluation.

With regard to PhD students their number was five at the time of the report (and is now four), which is close to the limit authorized with regard to the ratio between PhDs and scientists with HDR.

5- « The role played by the many scientific collaborators in this team is not always clear »

We apologize to the committee, and to these collaborators, if our report did not make clear the importance of their participation.

There are four scientific collaborators. One was the founder of one of the forming groups and has retained a considerable interest to the internal scientific debate around mitochondrial function, with special emphasis on « UCPs ». The three other collaborators are MDs or hospital biologist with important medical duties but also research activities that are essential for the translational aspect of the team project. One collaborator spend two full days a week in the laboratory and is a key element for the ongoing project on human complex V defects. One collaborator is in charge of the diagnosis of mitochondrial diseases in La Pitié hospital, which has been initiated and still is a major interest of one of the founder groups. The third collaborator is a surgeon who is a long-time collaborator of one of the founder groups and is essential to the development of the project on pathophysiology of mitochondrial fatty acid oxidation and bioenergetics in human obesity.

Team 8 :	Iron, Oxygen and Energy Sensing in Pathophysiology
Name of team leader:	Ms Sophie VAULONT and Mr Benoit VIOLLET

REPLY TO THE COMMITEE

The group would like to thank the committee for the recognition that the group is “at the forefront of research in the field of iron metabolism and homeostasis and is continuing to make seminal contributions to this field and more recently, in the related fields of oxygen and energy homeostasis” and that “unique profile of research places them amongst the leading laboratories in this particular field “. Nevertheless, we would like to discuss specific points emphasized by the committee.

For the committee, the project proposition was too extensive considering the expected size and funding of the lab.
Importantly, concerning this issue, since the evaluation in January 2013, the group has been successful in obtaining two grants from the labex GREX (2 X 40 Keuros), one grant from the IDEX PRES Paris Sorbonne (50 Keuros) and one postdoctoral fellowship from the region Ile de France (120 Keuros). In addition, new contracts with pharmaceutical companies are under negotiation.

Weaknesses and threats:
A general feeling of the committee was that some projects were exclusively developed to generate new tools or models for collaboration. The team should concentrate on their own projects, rather than collaborations to further increase the quality of the publications

The group regrets to have given this impression to the committee. Actually, generation of mouse models was never conducted as a specific aim *per se* for the sole purpose of collaboration. A large part of our research activity has always been focused on the development, characterization and exploration of unique animal models to answer original and scientific questions of pathophysiology and to test potential therapeutics. During these last years, the generation of these models helped us to gain into visibility in our particular fields. Then, the growing interest of the scientific community for these mouse models gave us the opportunity to establish an expanding international interaction network (participation to European networks, invitation to international meetings…). Although some of these collaborations involve sharing of materials or new tools, many of them are far beyond the only sharing of the material with a strong involvement of the group. According to the group, these collaborations have allowed to strengthen their competitive position, to reinforce their international visibility and to set up successful collaborative projects with leading laboratories.

The ERC granted scientist should become an independent team leader.
The ERC funding has been an extremely successful boost to develop an original project relying on a high synergy and expertise of team members. As recommended, the ERC granted scientist will become an independent team leader and this should constitute a first step toward a reflection for team restructuration.

Reply to Team-by-team analysis

Team 9 : Oxidative stress, cell proliferation and inflammation

Name of team leader: Mr Frédéric BATTEUX

Workforce

The team Workforces is somewhat different from what is stated in the team-by-team analysis
N1: Permanent professors and similar positions **Number as at 30/06/2012 is 6 (2.5) instead of 6 (2.8)**
Number of Research Supervisor Qualifications (HDR) taken **is 2 instead of 0**

Assessment of scientific quality and outputs

We fully agree with the committee that our work is translational, but
1) not far from being beneficial for patients since 4 clinical trials have been performed since 2009 directly based on our research and patents

- Three have explored the role of the redox modulators, mangafodipir on cancer. One of them that describes the mechanism and the prevention of oxaliplatin-induced peripheral neuropathy in cancer patients, is in revision in the Journal of Clinical Investigation
- One clinical trial has been approved in February 2013 to evaluate the role of arsenic trioxide on scleroderma. This trial, financed by a small pharma company Medsenic, will take place at Cochin Hospital and is based on two papers that we have published in 2012 on this topic (Kavian Arthritis Rheum 2012, J Immunol 2012).

2) If our scientific questions always arise from medical problems, our contribution to basic science is exemplified by several basic-oriented publications: Sci Transl Med (1 paper), PloS pathogens (2 papers), Arthritis Rheum (9 papers) or J Immunol (4 papers)

Assessment of the team's academic reputation and appeal

The unit is also affiliated to another DHU program: "*AUToimmune and HORmonal diseaseS*" Head C Boitard.

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

No comments

Assessment of the team's organization and life

Our group has been created in 2009 and affiliated to the University. At that time we were not affiliated to the Cochin Institute. In order not to remain isolated, our team has made its best efforts to join the Cochin Institute first as a partner in 2011, then as an affiliated unit in 2014. Since 2011, F Batteux has been a member of the board of the department "development, reproduction and cancer" at Cochin Institute. This has facilitated the participation of members of our group in the various thematic groups or journal club existing within the institute, and our students have had the opportunities to present their works in the "development, reproduction and cancer" department meeting,

Assessment of the team's involvement in training through research

No comments

Assessment of the five-year plan and strategy

ROS and ovarian cancers (OC): As mentionned in the oral presentation (slide n°23) since we are members of the Gyneco-arcagy network, we have access to a large number of primary tumor cell lines to evaluate TOR and ERK inhibitors *in vitro*. Our work in vivo will focus on the NRF2-KEAP1 pathway which is a key regulator of RedOx sate in cancer cells and is itself regulated by ERK and TOR pathways. The use of genetically - modified cancer cells will allow us to study the role of this pathway in ovarian carcinoma sensitivity to chemotherapy *in vivo*. The use of originally designed ROS modulators will be tested.
The role of the ROS modulators magafodipir to counteract chemotherapy side effects of chemotherapeutic agent has been published by our group (A Laurent Cancer Res, 2005, Alexandre, JNCI, 2006); a clinical trial has been performed to evaluate its effects on oxaliplatin induced peripheral neuropathy. In collaboration with a CNRS neurophysiology team at Gif sur Yvette, we have performed electrophysiological and confocal microscopiy analysis on a mouse model of oxaliplatin-induced neuropathy to determine the mechanism of the neuroprotective effect of mangafodipir. These results are in revision in the Journal of Clinical Investigation. This demonstrates that our team is also able to collaborate with basic scientists to go more in depth into the mechanism of ROS mediated diseases.

ROS and inflammatory genital tract disorders: We thank the committee for its evaluation on our project on the role of Dxl5/FoxL2 on endometriosis however, this project is less speculative than mentioned in the team-by-team analysis, since a preliminary transcriptomic analysis confirmed by SiRNA data gained by D Vaiman group and presented in the oral presentation (slide n°20) has shown the dysregulation of this pathway in endometriosis.
We agree that the presence of autoantibodies does not indicate *per se* that they are responsible for the phenomenon. That is why we have indicated in the oral presentation (slide n°19) that functional assays will be performed to test their potential cytotoxic or activating effects on purified stromal or epithelial cells.

ROS, infections, inflammation genital tract : A mouse model of Syphilis has been described by Klein (Nature, 1980). Intradermal injection of *T. pallidum* in C3H/HeJ mice induces transient prominent lesions at the site of inoculation, then the spreading of the spirochete all over the organism. This model will allow us to infect mice and monitor the spreading spirochetes through the organism, especially in the placenta of pregnant mice. Knockout mice with various immune statuses will be used to define the immune response during infection and particularly congenital infection.

ROS and skin. -I- Skin cancer: as stated in the written report, this subproject will be performed by one AP-HP fellow in virology who has defended her PhD thesis on this topic in september 2012. She will be helped by a technician (L Cantero) under the supervision of F Rozenberg, professor of virology. This work will be performed in collaboration with a team at Pasteur Institute

ROS and skin. -II- Skin inflammation: The discovery of the overexpression of polo-like/Aurora/CDC25 pathway in fibroblasts from HOCl-exposed mice come from the transcriptomic analysis of diseased fibroblasts from the skin of our sclerodermic mice and their comparison to normal skin fibroblasts. It is clear that this strategy is a fishing expedition by nature. However, the discovery of highly deregulated pathways involved in fibroblast proliferation, ROS modulation, fibrosis or angiogenesis are highly relevant to scleroderma both in mice and human and prompt us to investigate those pathways more in depth.

ROS and skin. -III- Skin inflammation of infectious origin. To date, several methods can be used to differentiate *P. acnes* strains. The most frequently used are based on biochemical characteristics and specific antibody recognition. *P. acnes* strains are distributed in 5 biotypes and two serovars type I and type II (Johnson and Cummins 1972). However, molecular typing methods like RAPD, PFGE, or the use of RNAr 16S do not appear to be reproducible and are not powerful enough to allow compare strains (Perry 2003; Oprica 2004; Rossi 2006).
The use of the RecA and Tly genes have permitted to differentiate 2 groups within the type I : IA et IB, and we propose to add a MLST panel currently in development with the genes lake, cob, osc, coa, zno, gms, pak, fba and cel. Using MSLT analysis to distinguish among *P. acnes* strains population, we will determine the most appropriate markers for the identification of the more « virulent » *P. acnes* strains and correlated with their capacity to induce proinflammatory cytokine production and ROS.

Conclusion

We thank the members of the committee for the helpful evaluation of our work and projects. We fully agree that our scientific questions always arise from medical problems with the following goals:

1) to explore new therapeutic opportunities for patients (as exemplified by 5 patents and 3 trials directly related to our research performed since 2009)
2) to go further into the mechanisms of how our transverse theme : “reactive oxygen species” impacts the pathophysiology of the diseases (as exemplified by basic papers published since 2007 by the team : Sci Transl Med (1 paper), PloS pathogens (2 papers), Arthritis Rheum (9 papers) or J Immunol (4 papers).

We fully agree with the recommendation of the committee that our novel affiliation within the Cochin Institute will favour interactions with basic scientists to go more in depth into the mechanisms underlying the pathophysiological processes of the diseases we investigate, while providing to our colleagues scientists our expertise on ROS and in medical and translational research. This has already started since 2011 and will be amplified.

Department "Reproduction, Development, Cancer"

TEAM E14
"Study of normal and pathological hematopoiesis"

Team Leaders: Didier Bouscary, Patrick Mayeux

Answer to the AERES comments

We acknowledge the reviewers of the AERES for their constructive comments and we would like to answer two points regarding the "weakness" that they have identified.

1- We perfectly agree that it is necessary for us to develop further in vivo (mouse) models and especially xenotransplantation models. We mentioned ourselves this point in the report that we transmitted to AERES prior to the evaluation visit. Nevertheless it should be noticed that members of the team that will merge in only one team for the next contract, are perfectly trained to these methods (see Lauret et al, Leukemia 2004). So, the development of these methods will be strongly facilitated by the new composition of the team. Moreover, we have right now started actions to develop this aspect in our lab: one researcher of the lab with permanent position will spend one year starting from September 2013 in a French laboratory that developed xenograft methods in order to learn and to bring back this knowledge in our team, another researcher, also MCU-PH in the team, will spend one year in Boston to work on animal models of acute lymphoid leukemia and a new lab technician (IE INSERM) that joined our team two month ago, is currently training to be habilitated for mouse handling; she will be in charge of in vivo mouse projects, especially those that focus on progenitors / macrophages interactions during erythropoiesis and also in leukemia.

2- We understand the concern regarding the risk of the development of two separate groups inside the team, each being directed by one of the team leaders and we will be vigilant to avoid this situation. Nevertheless, we think that this is unlikely, especially since several PIs simultaneously develop projects that are connected to the "erythropoiesis" part of the team and to the "leukemia" part. Three examples can illustrate this point: 1- involvement of GAS6 is studied both in the context of erythropoiesis (crosstalk inside the erythroblastic island) and in the context of leukemia (resistance to apoptosis), 2- one of the team leaders who is mainly involved in erythropoiesis studies also directs the PhD thesis of a student who works on the mechanisms of action of the Pim2 kinase in acute myeloid leukemia, 3- a project has recently been funded by the SIRIC- CARPEM regarding the roles of Pumillio and TET2 in MDS. This project gathers PIs working mainly on the "erythropoiesis" projects and others working mainly on the "leukemia/HSC" projects. So, the two parts of the team are strongly interconnected and the risk that they function separately is unlikely.

Team 28

Biology of Phagocytes

Florence Niedergang

Errors to be modified

- Page 103 : « The team leader has also published a number of review articles (including in Nat. Rev. Microbiol.), […]

F. Niedergang has not contributed to a review in « Nat Rev Microbiol ». She was instead invited to write reviews in « Traffic » and « Immunobiology ». The text should be modified accordingly or the name of journals should be removed.

- Page 104 : « In addition, she has a strong commitment to teaching, and although she might step down from part of her teaching, […]

F. Niedergang indeed was heavily implicated in teaching but she has already stepped down: teaching was 100h until 2010, 50h in 2011, but only 12h since the beginning of 2012, as mentioned in the activity report.

Additional information

- We recently obtained the selective grant “Equipe FRM” (300 keuros for 3 years).

- We agree that technology transfer has to be developed. Indeed, we believe that some of our experimental models were recently ready for translational approaches. We obtained in February 2013 a collaborative ANRS grant (2013-2015, with A Brelot, Institut Pasteur and F. Perez, Institut Curie) entitled “Dynamic study of CCR5 secretion and inhibition of its transport to the surface of HIV target cells », with the objective to identify inhibitors of HIV entry.