CRC - Centre de recherche des cordeliers

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Centre de Recherche des Cordeliers

CRC

Under the supervision of the following institutions and research bodies:

Institut National de la Santé Et de la Recherche Médicale

Université Paris 6 - Pierre et Marie Curie

Université Paris Descartes

January 2013

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

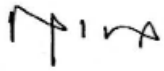
Research Units Department

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 following grades:

- Grading table of the unit: Centre de Recherche des Cordeliers

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

- Grading table of the team 1: Mineralocorticoid receptor: pathophysiology and therapeutic innovations

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

- Grading table of the team 2: Pathophysiology and therapeutics of vascular and renal diseases related to diabetes and nutrition

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

- Grading table of the team 3: Renal genomics, physiology and physiopathology (New name: Metablism and renal physiology)

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

- Grading table of the team 4: Intestine: nutrition, barrier and diseases

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

- Grading table of the team 5: Molecular Oral Pathophysiology

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

- Grading table of the team 6: Epigenetic and environment regulation of complex phenotypes

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

- Grading table of the team 7: Cellular and clinical pathogenesis of diabetes

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

- Grading table of the team 8: Complement and Diseases

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

- Grading table of the team 9: Apoptosis, Cancer & Immunity

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

- Grading table of the team 10: Bacterial structures involved in antibiotic resistance modulation

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

- Grading table of the team 11: Cancers, Immune Control and Escape

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

- Grading table of the team 12: Integrative Cancer Immunology Laboratory

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

- Grading table of the team 13: Immunopathology and therapeutic immunointervention

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

- Grading table of the team 14: Physiopathology of ocular diseases

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

- Grading table of the team 15: Cell death and drug resistance in lymphoproliferative disorders

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

- Grading table of the team 16: Information Sciences to support Personalized Medicine

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

Evaluation report

Unit name:	Centre de Recherche des Cordeliers
Unit acronym:	CRC
Label requested:	INSERM, Université Pierre et Marie Curie, Université Pierre Descartes
Present no.:	UMR-S 872
Name of Director (2012-2013):	Mr Hervé FRIDMAN
Name of Project Leader (2014-2018):	Mr Pascal FERRÉ

Expert committee members

Chair:	Ms Yannick Le Marchand-Brustel, Université de Nice, France
Co-Chairman:	Mr Pedro ROMERO, Lausanne, Université de Lausanne, Switzerland
Experts:	Mr Alain BAULARD, Université de Lille
	Mr Rudy BILOUS , Université de Middlesbrough, UK
	Mr Christophe CAUX, Université de Lyon
	Mr Hugues CHAP, Université de Toulouse (CNU representative)
	Mr Pierre COULIE , Université Catholique de Louvain, Belgique
	Ms. Helène DUTARTRE, Université de Lyon
	Mr Martin GLENNIE, University of Southampton, UK
	Mr Christian HAMEL, Université of Montpellier
	Mr Jens LEIPZIGER, Université of Aarhus, Denmark
	Mr Jean-Claude MARTINOU, Université of Genève, Switzerland
	Mr Pierre PACAUD , Université de Nantes
	Mr Fred PACCAUD, Université of Lausanne, Switzerland
	Mr Hans-Ullrich PROKOSCH, University of Erlangen, Germany

Experts:

Ms Marie-Paule ROTH, Université de Toulouse

Mr Jurg SCHIFFERLI, University of Basel, Switzerland

Mr Jean-François TANTI, Université de Nice (CSS INSERM representative)

Ms. Laurence VICO, Université de Saint Etienne

Scientific delegate representing the AERES:

Mr Bernard DASTUGUE

Mr Daniel OLIVE

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

Mr Paul INDELICATO, Université Paris 6 Pierre et Marie Curie

Ms Sylviane INNOCENCIO, INSERM

Mr Stefano MARULLO, Université René Descartes

1 • Introduction

History and geographical location of the unit

The CRC was founded as an emerging Centre in January 2007, on the "Cordeliers" site, foreseen as a site structure integrating all scientific teams of the Cordeliers Campus. It is situated in the heart of Paris, and houses the schools of medicine of University Pierre et Marie Curie (Paris 6), and René Descartes (Paris 5). It is in close proximity to many major institutes (Institut Curie, Institut Cochin, Collège de France) and of many hospitals (HEGP, Hôtel Dieu, Cochin, La Pitié Salpêtrière, Saint Louis, Garancière). The Centre, which originated from IFR 58, included 18 teams, grouped in 4 research axes, which were mostly local teams. This resulted in a pluridisciplinary structure, this characteristic being considered as a strength rather than a weakness. The first contract period was used to structure the Centre, to develop platform facilities, to organize the administrative staff, and to create a centre of excellence in modern physiology and physiopathology. The Centre's life was organized through scientific animation and adequate governance. This Center is under the "Tutelles" of INSERM, and the universities Pierre et Marie Curie and Paris Descartes. During this period the different research teams were consolidated into two departments (Nutrition, Metabolism and Differentiation for one department, Immunology, Cancer and Inflammation for the other one), with some arrivals, and some teams leaving for other places.

Management team

The CRC was directed during the 2008-2013 contract by Mr Wolf Herman FRIDMAN, with Mr Jean CHAMBAZ as the deputy director. The current project leader is Mr Pascal FERRÉ, with Mr Guido KROEMER as the deputy director. This arrangement is essential in order to ensure the equilibrium between the two departments and the fostering of future productive synergies. Strengths of the project leader are notably his deep knowledge of the scientific and administrative environment in a complex organization with three trustee institutions and his decision to focus exclusively on the direction of the Centre. Indeed, he chose to relinquish the leadership of his research team in order to maintain impartiality. There is an internal rules brochure that should be of help to the future leader and his management team. There is a scientist responsible for each department (one man, one woman). There is an administrative manager, a general secretary, a core facility manager and a manager for Hygiene and Security aspects. The Director is assisted by a Management Committee, which can be extended to all team leaders from time to time. There is a Centre Council, including representatives of all staff categories. An International Scientific Council (which Président attended the AERES site visit) meets every two years, reviewing the written projects before submission to AERES.

The organisation chart is roughly similar to the organization which prevailed during the last contract and proved to be efficient and satisfactory. Clearly the project leader is strongly committed to bring a collegial management involving all the team leaders.

AERES nomenclature

SVE1, LS 1, 2, 4, 6, 7

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	83	54	53
N2: Permanent researchers from Institutions and similar positions	62	47	47
N3: Other permanent staff (without research duties)	107	91	91
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	2	2	2
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	53	34	34
N6: Other contractual staff (without research duties)	32	3	3
TOTAL N1 to N6	**339**	**231**	**230**

Percentage of producers	***99 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	76	
Theses defended	125	
Postdoctoral students having spent at least 12 months in the unit*	66	
Number of Research Supervisor Qualifications (HDR) taken	24	
Qualified research supervisors (with an HDR) or similar positions	99	

2 • Assessment of the unit

Strengths and opportunities

High scientific quality of the participating teams as attested by the level of publications.

Multiple CRC teams form part of excellent networks, namely Labex ImmunoOncology, CARPEM, PACRI, IHU (ICAN).

National and international recognition of many members of CRC.

Authentic translational activities towards clinics, affiliation with multiple large Paris hospitals, numerous MD are members of research teams and have double affiliations with hospitals.

Large number of patents, and creation of a start up.

High capacity for the teams to raise funds.

Attractiveness to PhD students. Strong involvement in teaching. Very active training activities in medicine, dentistry and sciences, participation with leading doctoral schools.

Excellent gender balance among the team leaders.

Excellent core facilities (animal and imaging facility). A strong will to obtain quality certification.

Excellent and original mouse models and unique exploratory metabolic platforms.

Arrival to the CRC of novel teams.

Adequate rearrangement of some teams within the CRC.

The project is enthusiastically endorsed by all the research stakeholders at the CRC.

The CRC is at the forefront of research in both cancer immunobiology and physiology. There are golden opportunities for further interdepartmental interactions eg cancer metabolomics or innate immunity, inflammation and cardiovascular and metabolic pathologies.

The collaborative grants initiative has been received very positively and should be continued.

Weaknesses and threats

The departure of one team expert in "Nutrition and Obesity" may weaken department I, but a strong presence remains through the IHU excellence program.

A relatively large number of scientists and technical staff will retire during the next contract.

Insufficiency of technical staff, more specifically in the teams.

Multiplication of layers of institutional and funding initiatives bring increased funding but at the same time pose new challenges for the leadership.

The cost and increasing regulatory burden on animal experimentation.

Necessity to raise a large amount of money for each team. Further the new French law imposing strict limits to the duration of non permanent positions rendering the recruitment and stability of scientific staff (both scientist and technicians) which is difficult and not very efficient, may threaten the international competitiveness of the CRC. The complexities of the French administrative system is also a threat for the future of the CRC.

Recommendations

To continue the drive to recruit young researchers (CR or assistant professor positions).

To be aware of preserving the unique know how accumulated at the CRC, for example for specific exploration techniques in animals.

To attract excellence through dedicated calls (Avenir, ERC…type of grants), keeping in mind the search for novel opportunities to foster interdepartmental initiatives.

To strive to promote the continued and productive development of the two departments.

To increase the recruitment of international PostDocs and PhD students.

To publish in the best journals, with a general audience as often as possible.

To promote new initiatives to enhance communication at all levels of the Centre.

To stimulate exchange in English (internal and external seminars, journal-clubs all in English).

To establish mentoring programs for both scientific excellence and managerial skills in the case of team leaders.

To increase the CRC international visibility through *eg* organization of international meetings, refurbishing of the webpage.

To increase the interactions and cohesion of the trainees (PhD students, postdoc from both departments), through the creation of a club with specific scholar activities, *eg* journal clubs.

To envision the possibility of changing the CRC initials: indeed the profile of the CRC was compromised by its initials which in the UK and USA translate into **C**linical **R**esearch **C**enter.

Recommendation to the parental institutions: to maintain a strong financial support (both money and technical and researcher positions) to the CRC.

3 • Detailed assessments

Assessment of scientific quality and outputs

The CRC was founded as an emerging Centre in January 2007, on the "Cordeliers" site, foreseen as a site structure integrating all scientific teams of the Cordeliers Campus. This resulted in a pluridisciplinary structure, this variety being considered as a strength rather than a weakness.

The production of CRC has been excellent with 1100 papers since 2007, 190 of which were published in journals with an IF >10 and 300 in journals with an IF between 5 and 10. It should be noted that nearly all teams published in journals with a large audience and in the best journals of their specialty. It should also be noted that the IF of the best journals in dentistry, in eye research, or even in diabetes, are much lower that the IF of journals in other fields of biomedical research, for instance molecular cancer, immunology or genomics.

The research is organized in two departments (for clarity of the present report, teams have been relabelled from Team 1 to Team 16, regardless of team labelling associated to the ending period):

Department I: Physiology, Metabolism Differentiation

This department included 10 teams (9 for the coming period) involved in the study of various organs (kidney, liver, eye, muscle, intestine, tooth) in relationship with various pathologies among them diabetes, obesity, hypertension, kidney diseases. This research has strong collaborations with various hospitals (St Louis, Pitié Salpétrière, Hotel Dieu…).

The research performed in this department has led to major discoveries, as outlined in the various team descriptions, the development of original animal models, the development of original animal physiological phenotyping, and to the proposal of new therapeutic approaches, already tested in patients. The CRC thus appears as a centre of excellence with a unique expertise in physiology and physiopathology, most teams studying integrated functions at the tissue, organ and organism level. The development of core facilities, and more specifically the opening of a modern animal facility with the development of technical platorms to study renal function and metabolic diseases has played a key role in this research.

Four major discoveries are briefly outlined here:

- Mineralocorticoid and retinal diseases. (J Clin Invest). They discovered the role of the mineralocorticoid receptors (MR) in central serous chorioretinopathy (CSCR), a vision-threatening eye disease with no validated treatment and unknown pathogenesis. These studies led to successful treatment of patients with a specific MR antagonist (Collaboration Team 1 and 17).
- Renal physiopathology (J Clin Invest.). They demonstrated that the extraparathyroid calcium receptor (CaSR) is a direct determinant of blood Ca^{++} concentration independent of PTH, and dissected the mode of action. This study provides evidence that the use of CaSR inhibitors should be considered as a therapeutic option for the care of patients with parathyroid disease (Team 3).
- Intestine physiopathology (Gastroenterology). They identified the cellular prion protein, PrP^c, as a component of desmosomes, key actors in the establishment and maintenance of cell-cell junctions in the intestine. They showed that desmosomal PrP^c plays a fundamental role in the conservation of the intestinal epithelium barrier function and participates in the mechanisms that link intestinal barrier integrity and susceptibility to intestinal inflammation (Team 4).
- Liver physiopathology (steatosis). (J Clin Invest). Obese mammals are characterized by an accumulation of liver fat (triglycerides) known as steatosis. Lipogenesis is an insulin-stimulated process which is paradoxically stimulated in the liver of insulin resistant obese mammals. This work provides an explanation for this paradox by showing that the endoplasmic reticulum (ER) stress is able to activate the transcription factor SREBP-1c. Attenuation of the ER stress in liver reduces hepatic steatosis and reverses the metabolic dysfunctions in the liver of obese rodents (Team 8).

The teams also developed interface programs and research. Of particular importance is the joined effort of five teams to create the Institute of Cardiometabolism and Nutrition (ICAN). This is a major source of recruitment of post doctoral fellows for the next years, and a major opportunity to develop strong link with clinics.

Department II: Cancer, Immunology, Immunopathology.

It is composed of 7 teams, 135 people, working in the fields of cancer, inflammation, cell survival, immunology and immunopathology. All teams maintain strong connections with hospitals, mainly those located in proximity of the Center (Hôpital Europeen Georges Pompidou, Hotel Dieu/Cochin, Institut Gustave Roussy and La Pitié Salpêtrière). The scientific output of this department has resulted in 200 articles published per year in peer reviewed journals with an H factor of 68. Major contributions have been the following:

- The demonstration that immune cell infiltration in the primary tumor predicts clinical outcome in colorectal cancer patients (using two cohorts of primary tumors studied totaling 959 patients, (J Clin Oncol. and Nat Rev Cancer) as well as in lung carcinoma patients (Cancer Res). These studies have led to a major and broad international collaboration to validate immunohistopathological traits as predictive biomarkers and even as novel tools for tumor staging (immunoscore).
- The identification of a link between cancer cell ploidy and immune surveillance. Hyperploid cancer cells become immunogenic via the exposure of calreticulin at the cell surface as a result of a constitutive endoplasmic reticulum stress response. An immunosurveillance process exerts potent immunoselection against hyperploidy in carcinogen- and oncogen-driven tumors (Science).
- The elucidation of molecular determinants of immunogenic cell death elicited by anticancer chemotherapy. Multiple studies have led to the formulation of a model of immunogenic cell death requiring three key molecular elements, namely the exposure of calreticulin at the cell surface resulting from the ER stress response, the translocation to the cytosol and secretion of HMGB1 and the release of ATP. These results have been the object of numerous scientific publications, a good fraction of which in top ranked journals (for example Science).
- The identification of a gain of function mutation in the complement C3 component near the the factor B binding site. This constituted the description of the first case of a direct gain of function of the C3 convertase associated with the atypical haemolytic uraemic syndrome (Blood). The same group published a game changer set of observations in anti-complement therapies with the use of eculizumab, a monoclonal antibody targeting the complement component 5, for atypical haemolytic uraemic syndrome and C3 glomerulopathies (Nat Rev Nephrol).
- The demonstration that CD47 engagement in chronic lymphocytic leukemia cells is a new and original approach to trigger caspase-independent programmed cell death of malignant B-lymphocytes, even those from chemotherapy-resistant leukemias (Leukemia).

It should be noticed that the arrival of the team led by Mr Guido KROEMER is a very strong point for the Centre, and more specifically for this department. The LABEX of immunooncology was created in 2011 under the auspices of University Paris Descartes, composed of 7 research laboratories among which three are part of the Centre. Some teams of this department are also members of the PACRI network of excellence and the CARPEM site on integrated research in cancer.

Assessment of the unit's academic reputation and appeal

The unit’s academic reputation and appeal is excellent. Some teams have joined the centre during the last contract. Not least, Mr Guido KROEMER is joining the Centre in 2012, with his team, certainly contributing to the recognition of the Centre at a national and international level. Many team leaders are internationally recognized in their field, as evidenced by their list of invited conferences. Five new teams have joined the CRC during the last contract.

As will be detailed in the team by team analysis, many CRC members are involved in European contracts, have received grants from ANR, NIH, and from various institutions (national or international). They participate in many editorial boards of journals.

There are foreign postdoctoral researchers, although their number should increase in the next contract (for example through the ICAN)

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

The Centre also developped strong translational activities. To cope with the difficulties which could be due to the various parental institutions, there is a single entry for industrial contracts, patents are managed by INSERM through an agreement with Inserm Transfer and with the transfer offices of the two Universities.

Most of the teams (see details in each team evaluation) have partnerships with industry.

Since 2008, 36 patent applications were filed and deposited. A start up was created for ophthalmology development.

One of the major aspects is the strong interaction with clinics. A large number of medical doctors, and dentists are working within the CRC teams, and some researchers have a “Contrat d’interface” with a hospital. Many PHRC grants have been obtained by members of the CRC.

Scientific outreach towards wider society is also developed: for example, the center opens the labs to young secondary and high school students once a month, with a minicongress held at the end of the year.

Assessment of the unit's organisation and life

The Director and the Deputy Director are assisted by a Managing Committee, which can be extended to include all team leaders from time to time. There is a Centre Council, including representatives of all staff categories. An International Scientific Council visits every two years and their recommendations have helped the Centre in formulating its scientific policy. The general scheme of the actual CRC management will be continued with some relatively minor modifications. The project leader has been appointed following an international call. The involvement of the project leader in the CRC site, as the leader of a very efficient team in the ongoing contract also largely involved in teaching, will help him in the future conduct of his responsibilities. The Deputy Director will be Mr Guido KROEMER, and thus a good balance between the two departments should be obtained.

In order to develop the Centre "spirit", a great emphasis was given to scientific animation and a good governance. The important work of the preceding director has to be acknowledged in that he managed to create a functioning centre from the various units previsouly located in the same geographical site.

The development of core facilities has been a major achievement during the previous contract, and has led to the opening of three major units: A functional exploration centre, a genotyping and biochemical centre and a cellular imaging and flow cytometry centre. The opening of the animal facility was a major goal of the present CRC Director and required a tremendous effort from trustees (4.5 M€). It now allows state of the art exploration of original animal models, for example for renal function, cardiovascular function, metabolic function, ophthalmology and orofacial pathology. The facilities are opened to the CRC groups and to external users. Users can receive training and assistance.

The CRC has offered the possibility to award initiative programs: four grants of 50 000 euros each were awarded to young scientists in order to support transdisciplinary collaborative research between departments and teams, which have already led to high level discoveries and publications (JCI, ATVB…)

The committee of experts had the opportunity to separately meet the various staff categories: Technical staff, PhD students and post doctoral fellows, and non PI researchers. It is clear that the project is enthusiastically endorsed by all the research stakeholders at the CRC. They had very positive comments on the general CRC organisation, the core facilities, and the administrative organisation. It appears that a larger effort should be made to increase collaborations between the various teams and departments, and to improve communication at all staff levels.

The technician staff was very positive about the role of the technical staff committee, comprising Centre Council members and scientific and technical staff, which meets twice a year and decides on applications for promotion of the technical staff at the various institutions.

Assessment of the unit's involvement in training through research

The Centre has delivered an important training activity since 125 PhD have been obtained during the contract (75 pPhD students were present in the Centre as of June 2012). It is of important to note that many members of the CRC are professors or assistant professors and involved in teaching in partner Science, Medicine, and Odontology faculties.

The Doctoral schools include in particular:

- ED 394, Physiology and Physiopathology, Paris 6
- ED 392, Life Diversity, Paris 6
- ED 516, Biochemistry, Biotherapy, Molecular Biology, Infection, Paris 7
- ED 436, Drug, Toxicology, Paris 5
- ED 393, Public Health, Paris 6

Various activities are proposed by the CRC to their PhD students (organisation of a one day meeting each year), although those activities should be developed further. They participate in congresses, and publish regularly. Core facilities are also used for practical workshops on cell imaging, transgenesis, cell sorting, for example.

Students largely have a scientific background, MDs, PharmDs, or dentists, which is an indication of the strong translational activities, and of the active training through research.

The technical staff has also an easy access to training through the institution’s proposals (Continuous training).

Assessment of the five-year plan and strategy

The scientific project is in the line of the previous programs. It should be noted that the project leader was appointed only in April 2012, making the time period to prepare the project prior to the site visit very short. This did not allow him sufficient time to publicize an international call in order to try to attract new teams. The project is thus based on the existing scientific potential, although some reorganization has taken place.

Two departments will be maintained, with a slight modification of new team 14, working on the physiopathology of ocular diseases joining department I, due to its strong interaction with Team I.

Detailed Department I strategy :

Department 1 has unique characteristics, as already mentioned. Physiology and physiopathology are studied in various organs: liver, kidney, intestine, teeth, eyes for example. The Integrated animal models are or will be developed, taking advantage of the phenotyping capacity of the animal housing facilities. Translational research will be developed from experimental models to clinic, and vice versa from bedside to experimental models. This will be made easy through the very active interaction of MDs with a wide range of specialties and Dentists, with various teams, and the close connections with several hospitals. The IHU (ICAN, Institute of Cardiometabolism and Nutrition) will be an important link, and it should be noted that 4 teams (out of 19) of the ICAN are part of the CRC. Diabetes is one of the major pathologies common to many teams in the department, with its various complications in the kidney, eye, and oral cavity.

Detailed Department II strategy:

The major characteristics of Department II are the ability to combine immunology, immunopathology and cancer studies directly in humans, particularly in cancer patients. The major goals are to find new prognostic and predictive biomarkers, to define new drugs or to reposition existing ones with improved biological activities and to design research-inspired novel strategies of immunotherapy. Unique assets in this department are the full access to large annotated collections of human tumours, a unique collection of blood samples (400) from patients with complement mediated diseases, high throughput analyses (stress pathways, immune microenvironment) and sophisticated mouse models. The strategy for research is condensed in three departmental joint programs: (i) the immune microenvironment and cancer, (ii) cancer cell death and effect of chemotherapy and (iii) immunopathology. This is a fully translational research extending all the way from clinical work to mouse models and using state of the art bio-informatics, many of them developed in house. Several teams are active contributors of the LabEx ImmunoOncology, including the leader and coordinator of this national excellence grant. In addition, several teams are also involved in the CARPEM, co-directed by Mr Hervé FRIDMAN (current CRC director), and PACRI, directed by Mr Guido KROEMER (future associate director of the CRC). In terms of management, the department will organize half-day thematic meetings on the joint programmes, quarterly Guest Lectures of the European Academy of Tumor Immunology, an annual International Conference on tumor immunology, in addition to seminars and half-day colloquia on hot topics. Multiple acquisition of equipment initiatives are programmed and the joint meetings with team directors include study of applications for new positions, equipment acquisition and joint applications for major funding.

Conclusion:

Since free space (700 m^2) will be available, the key actions will be to promote the arrival/recruitment of young scientists who could be able to develop within the CRC. It will be important to maintain a good equilibrium between the two departments especially following the arrival of Mr Guido KROEMER's team. The director also appears aware of the importance to encourage horizontal collaboration, to define common topics and promote concerted responses to calls, and to enhance the financing by the CRC of common projects between teams.

In conclusion, the project is very solid, and highly feasible. It takes full advantage of the major achievements of the current funding period and it aims at consolidating the two department structure and to build bridges between the two via highly original research on topics at the cutting edge of biomedical research. The synergy of the team projects is very good and has potential for further improvement. The Centre has acquired a solid national reputation and has emerged as a power house in physiology, metabolic diseases as well as in tumor immunobiology in the international arena. The drive to enhance its international profile and to make the Centre competitive in the two major fields of research that identify it today requires a continued leadership and extra sharperning of the focus of the research programs and its individual projects. In this regard, it is highly encouraging to find that the new leaders (Director and Deputy Director) for the next funding period starting 2014 are already well in place and powerfully represent their own CRC departments. It is important going forward to multiply the efforts to make this Centre visible not only, and foremost, at the scientific publication record but also in the new internet-based communication media. The next period will provide novel opportunities for the newly formed teams to consolidate and to recruit new members, ideally drawn from the excellent French ranks and by attracting talent from the United States and wider Europe. Management and governance have been excellent thus far and should continue to enhance the scientific and administrative coherence and productivity of the Centre. In this regard, it is important to state that the three bodies underwriting the Centre, INSERM, University Paris Descartes and University Pierre et Marie Curie continue to be engaged and deeply committed to the overall aims and strategy of the Centre.

4 • Team-by-team analysis

Team 1 : Mineralocorticoid receptor : pathophysiology and therapeutic innovations

Name of team leader: Mr Frederic JAISSER

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	0,5	0,5	
N2: Permanent EPST or EPIC researchers and similar positions	1	2	
N3: Other permanent staff (without research duties)	3	4	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	2	
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**8,5**	**8,5**	

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	3	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	3	4

• Detailed assessments

Assessment of scientific quality and outputs

The goal of team 1 is to define the role of aldosterone and glucocorticoids as well as their receptors (mineralocorticoid receptor, MR; glucocorticoid receptor, GR) in the cardiovascular and renal systems, in physiological and pathological settings. It develops integrated projects combining various approaches (cellular and molecular, as well as animal physiology with the generation and characterization of genetically modified mice) and human pathophysiology and therapeutic insights.

This work led to several major achievements in the field and placed the lab at the cutting edge of the research on this topic in the international environment including 1) in vivo evidence of a role of cardiomyocyte MR and GR in the generation of arrythmias, 2) direct role of vascular MR in the control of blood pressure, 3) direct evidence of the pathogenic role of vascular MR activation in the ocular choroid and successful translation to clinic to improve patients with central serous chorioretinitis, 4) *in vivo* pathophysiological effect of MR in the skin (keratinocyte, hair follicle) leading to a clinical trial.

The team has produced since January 2007, 42 original articles, including 20 originating directly from the group, 3 with an IF>10 (J. Clin.Invest, Circulation), 11 with an IF between 5 and 10 (Hypertension, FASEB J. J Am Soc Nephrol), 6 with IF< 5, 22 in collaboration and 10 reviews chapters or invited commentaries. The number of citations (without self citation) of the papers published since january 2007 is 357.

Assessment of the unit's academic reputation and appeal

The national and international visibility of the team is attested by several invitations for major conferences in national and international meetings (like the ESC 2010, ENDO 2011, the APS ENac-Aldo meeting 2011, EDTA 2012, ISH 2012). The team leader is also president of the European Section of the Aldosterone Council since 2009 and has co-organized several international conferences. He is member of the Editorial Board of the Endocrinology and Clinical Science journals and has been nominated International Fellow of the American Heart Association (FAHA) in 2011. The internationally visibility is also attested by the welcome of several foreign students, researcher and professors for sabbatics.

The team leader has been appointed as the Scientific Coordinator of the Pathophysiology section of the French National Research Agency. Since 2009 he has been appointed member of the INSERM Specialized Scientific Committee (CSS4, cardiovascular-renal-endocrinology) and has been member in the past of the Physiology section (CS66) at Pierre-Marie Curie University. He has obtained a “contrat d’interface” with the Nancy hospital.

The team is involved in several national (ANR Mirendo 2011-2014, ANR Mineraloret 2012-2014) and international projects (European grant 2006-2010, Leducq Foundation 2007-2012). It is also implicated in clinical research programs (DHOS Inserm 2008, EpleCsAT safety 2011-2012, Spirepi 2012, CRSC 2012-2013)

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

The team is very active in the dissemination of their results through intellectual Property protection and industrial partnership. They have filled five patents and obtained financial support from a special fund of INSERM-transfert (Proof of Concept Fund), of the national Research Agency (ANR-EmergenceBio) and the French public-sector institution dedicated to economic development (OSEO). They also obtained grants from industrials: CEVA santé, Genzyme; Bayer; Pfizer; and Biorad for a new NGAL diagnostic kit.

Assessment of the unit's involvement in training through research

Over the past five years, the team accommodated 10 Master2 students, 7 thesis in PhD school entitled “Physiologie et Pathophysiologie” of Paris 6, 3 of them have already obtained their PhD. Two are post-doc in Canada and Australia and one is hospital MD in China.

Researchers of the team are involved in teaching for scientific, engineers and medical students as well as residents. The team leader is currently part-time associate professor at the Reims Medical Faculty where he is coordinator of a Master module (« Animal models: insights into pathophysiology »).

Assessment of the five-year plan and strategy

The proposed project is the evolution and the continuation of the past activity and results of the Team 1. A novel direction concerns the role of MR activation as a deleterious factor in end-organ damages in cardiovascular as well as renal and eye injuries. This is associated with a sustained effort to analyze signaling pathway modulated by MR activation and to engage translational research dealing with validation of theranostic biomarkers of MR activation or novel therapeutic indications of MR antagonists.

The project is well constructed. The team has developed relevant collaborations (with clinical units for translational research projects and private partners for pharmacological projects) and original animal models to set up their projects with good chance of success. The evolution of the basic results previously obtained towards clinical project is relevant and well thought. The risks of the most part of the project are limited. The most risky part concerns the therapeutic innovations but undoubtedly deserves to be done as an application of their basic research.

The SWOT analysis is honest and realistic with most weaknesses underlined.

Conclusion

- Strengths and opportunities:

The members of the team are experts in the field, as shown by their international visibility and their participation into international networks (Leducq Network of Excellence, ECOS project with Chile). The place of the team in the international MR research area is also associated with the original mice models it has developed and its capacity to perform cardiovascular/renal/metabolic phenotyping. The team leader also shows a very strong capacity to obtain grants and funding (academic and private) and is strongly involved in scientific expert committees. The evolution of the research projects towards translational and clinical research, although challenging, seems to be a good and relevant choice

- Weaknesses and threats:

Regarding the competitiveness of the project, the main weakness of the team is its limited size,

- Recommendations:

It will require to rapidly recruit young full-time researchers, and to obtain strong external resources to support more postdocs.

Team 2 : Pathophysiology and therapeutics of vascular and renal diseases related to diabetes and nutrition.

Name of team leader: Mr Ronan ROUSSEL

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	4	
N2: Permanent EPST or EPIC researchers and similar positions	3	3	
N3: Other permanent staff (without research duties)	3.5	3.25	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	2	
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**11.5**	**12.25**	

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	3	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	7	7

• Detailed assessments

Assessment of scientific quality and outputs

There is a new team leader. The previous incumbent is an internationally acknowledged expert on vasoactive peptides. The FIA lists 175 publications and > 10,500 citations for him and 45 articles for the new team leader.

The team has developed novel expertise in exploring the role of kinins and vasopressin in vascular diseases, and diabetes and its complications in rodents. They have also discovered human gene polymorphisms with potential clinical significance. The team have demonstrated a conceptual and methodological maturity in their field with established tools to explore new ideas and directions.

67 publications including 53 original articles. Many of the publications are in high impact factor journals (Hypertension, ATVB, Circulation research, Diabetes, Faseb J...). Many have international collaborators. Much of the data has been presented at major international scientific congresses. Thus the quality of the work is of a very high calibre.

Assessment of the unit's academic reputation and appeal

Extensive international collaboration with the USA, Canada, Australia and Europe has been described. Nationally, extensive links between clinical research and scientific study are described notably with the DESIR, DIABHYCAR, and DIABHYCARGENE studies.

Two european contracts, one EU-ERC starting grant.

The previous director was a work package co-ordinator for the EVCM Excellent Network of the EUFP6 from 2004-9.

The team has hosted 3 visiting scientists (2 from the UK, 1 from Germany) and 5 post-doctoral students.

The Berliner Award for Excellence in Renal Physiology from the American Physiological Society was awarded to a team member in 2011

The scientific quality of the journals accepting articles and reviews from the team is very high.

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

Experimental – The Kallikrein knockout mouse is a significant development for experimental research.

Therapeutic – The KKS agonists are the subject of a European patent and of significant potential therapeutic benefit.

Assessment of the unit's organisation and life

The scientific objectives are coherent and logical. There is little detail of the governance and/or structure of the department, committees, premises etc however.

Assessment of the unit's involvement in training through research

Eight PhD students are listed, 5 awarded and 3 pending. Two to four Masters students are trained per year. One PhD stayed for a post-doctoral fellowship. The new leader is a Co-Founder of the Inter-University Diploma for Diabetes Care and a Steering Committee member for an international educational programme initiated from the International Diabetes Centre of the University of Minnesota, USA.

Assessment of the five-year plan and strategy

The proposal is in 3 parts and is on the whole a coherent and logical programme.

Part 1 – Role of Kallikrein and kinins in the progression of diabetic complications and ischaemic cardiovascular and renal diseases. This part is well described and builds upon the excellent established expertise of the group. Some areas are weaker, notably the aortic aneurysm study and the team may wish to concentrate on other aspects.

Part 2 – Vasopressin, diabetes and its vascular complications: clinical and experimental approaches. This is an ambitious and novel area of research into diabetes causation and its complications. There are concerns that the basis for this work is not fully established and this is acknowledged by the team in their proposal. We would suggest that more basic work to establish the hypothesis is undertaken before embarking on a large clinical research endeavour.

Part 3 – Determinants of vascular risk in diabetes. This part applies the research from Parts 1 & 2 into man by utilising established research databases, and developing new cohorts of people with longstanding diabetes. This is potentially very important and if the kinin agonists prove efficacious and safe then the implications for diabetes and cardiovascular disease therapy are significant. However, the team must be wary of potential confounders when attributing causation to association.

Conclusion

- Strengths and opportunities:

The team offers a unique opportunity to go from fundamental research to clinic. The part 1 proposal is well supported by previous work from the team. The resulting publications are of high quality. The research plan is thoroughly and comprehensively outlined and the essential tools are available. The research is likely to lead to important new discoveries. Part 3 represents a novel and relevant development for the team and complements the basic research. The clinical research expertise and SGLT2 project is to be commended for its pathophysiogical basis. There is a high level of International cooperation.

- Weaknesses and threats:

The role of vasopressin in the causation of metabolic disease and its complications is not completely supported by available data and this part is viewed to be of slightly higher uncertainty and risk. Some aspects of Part3 would have benefited from more detailed description of the methods.

Paucity of tenured technical staff.

- Recommendations:

The research activity of this group has a very strong clinical and translational perspective which is to be highly commended. It is advised to review some parts of the plan in order to strengthen the scientific basis.

Necessity to increase the number of tenured positions (for young scientists and technicians)

Team 3 :

Team name: Renal genomics, physiology and physiopathology

New name: Metablism and renal physiology

Name of team leader: Ms A. EDWARDS

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	
N2: Permanent EPST or EPIC researchers and similar positions	7	5	
N3: Other permanent staff (without research duties)	8.3	9.5	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2		
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**19.3**	**15.5**	

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

• Detailed assessments

Assessment of scientific quality and outputs

The scientific productivity of team 3 during the period 2009-2013 is outstanding and impressive. It is not the mere amount of publications and their citation impact that comes to mind. More importantly, it is the large number of truly relevant papers of this group that have contributed to a substantial revision of our understanding of how the kidney functions. To mention some, this network of researchers identified novel (or contributed to identification of) truly important players/proteins such as Rhcg and NHE4 for renal NH_4^+ handling, a novel Na^+ transporter in the apical membrane of the collecting duct (SLC4A8), important novel aspects of Ca^{2+} handling by the Calcium sensing receptor, the paracrine regulation of ion transport by tissue kallikrein or the role of basolateral K^+ channels (KCNJ16) in Na^+ absorption in the distal nephron. Also the progress in the understanding of how NKCC2 is regulated by trafficking events is seen as very valuable as this may lead the path to better understand and study the physiology of the thick ascending limb of Henle. Many studies offer an important translational persepective and contribute to our understanding of common diseases. A large number of papers have been published in the best international journals in this field (Kidney International, JBC, AJP Renal Physiol, Hum Mutat).

Assessment of the unit's academic reputation and appeal

This group has a long-standing and extremely well recognized international reputation in basic medical research in the area of renal membrane transport science. On a global plan it can be viewed as one of the few core activity centers in renal physiology. Many of the current members in some direct or indirect manner originate from a very strong French tradition in renal physiology. Many of the group members are well connected to other renal physiology research centers in Europe and abroad. A large network of international collegues and collaborators have close connections to the CRC group. Many publications are joint with colleagues from around the world.

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

The teams are using original research tools such as the COPAS sorter, which is one of the few in Europe. They accommodate visiting researchers to learn unique technical skills. In the report 7 contributions are listed that communicate the group's research results to a more general public. Thus, team 3 is actively participating in the interaction with their cultural environment. No patents are listed but there are only limited opportunities given the basic nature of their research and its focus on physiology. However,there are well established links with clinical teams in the partner University Hospitals.

Assessment of the unit's organisation and life

Team 3 has benefited from strong leadership by a nationally and internationally very well recognized researcher, who will retire during the next contract. There is an opportunity to develop new research directions with the appointment of the new leader. The group had about 30 members subdivided into smaller subgroups, each with their specific topic in renal reseach. A large repertoire of complementary technical expertise exists and has been beautifully exploited by the network. It is viewed that the local environment must have been very stimulating and large enough to generate such a high number of very valuable products. A local dynamic environment is viewed as one of the key prerequisites for very good research. In addition at least two members of the team of principal investigators are clinicians with ample experience for the translational dimension of their research areas.

Assessment of the unit's involvement in training through research

There are a large number of PhD and Masters students but little detail on the structure and quality of their training, nor of their future posts and careers. However, the research output of the team would suggest that they are very productive.

Assessment of the five-year plan and strategy

The chosen questions are all very interesting and relevant (Mechanisms underlying hypercalciuria? Formation of Calcium stones? The development of an integrated understanding if calcium homostasis?). The exact description of each sub-question could have benefitted from a more comprehensive reference list in order to support the often complex set of arguments. The group is going into a major restructuring period where several important and more senior researchers are leaving, but the appointment of the new leader provides opportunities for enhancing the current programme and developing new avenues of research. In the strategy, it is made clear that an array of novel collaborations will become part of the activity of team 3. The recruitment of new researchers or research sub-groups is not mentioned. A novel aspect of this research is the inclusion of mathematical modelling to renal physiology in order to strive for a more comprehensive understanding of complex problems.

Conclusion

- Strengths and opportunities:

This group has an outstanding momentum, productivity and reputation in the study of renal physiology. Substantial parts of the group continue to be active and new researchers have appeared to take up novel activities and challenges. A new leader has been appointed, with a lead in time to develop the team and its future direction.

- Weaknesses and threats:

The group has shrunk significantly. Several of the high quality papers in the preceding time have been produced by people that will not participate in the next 5 year project. Great care must be taken not to lose important technical and methodological expertise. The new leader is by training a chemical engineer and a transition to become a biologist appears necessary. The committee is reassured that the clinical perspective will not be disadvantaged. More “wet research” should be implemented and new groups could be encouraged to join and existing groups must also be strengthened.

- Recommendations:

A very well recognized and outstanding renal physiology research group is going into a significant transition period with less active researchers and a new leader. Great care must be taken to not lose this unique activity center and it is recommended to recruit more younger and also older researchers into the team. Continuing support for the team is strongly recommended.

Team 4 : Intestine: nutrition, barrier and diseases

Name of team leader: Ms Armelle LETURQUE

Workforce : Since Team 4 and former Team 9 are merging, the numbers are given as the sum of the 2 teams.

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	8	3	
N2: Permanent EPST or EPIC researchers and similar positions	8	5	
N3: Other permanent staff (without research duties)	5.3	5.3	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2		
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**23.3**	**13.3**	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	8	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	11	5

• Detailed assessments

Assessment of scientific quality and outputs

The new Team 4 will comprise some members of former Team 9 including the proposed team leader, and some members of previous Team 4. Both teams have produced original contributions in the field of intestinal physiology and pathology in relation to cardiometabolic diseases.

Former team 4 has made original contribution to:

1. The understanding of key steps of the intestinal secretion of triglyceride-rich lipoproteins (TRL) by the enterocytes. The scavenger receptor SR-BI was identified as an important factor for the sensing of dietary lipids in enterocytes. The importance of lipid droplets in enterocyte for the control of TRL secretion was demonstrated and their study in human suggests a defective catabolism of TRL in patients with metabolic syndrome. The different findings of the team validate the concept of lipid sensing by the enterocytes that participates in the regulation of TLR secretion. The work is important, solid and has clear relevance for intestinal lipid metabolism and cardiometabolic diseases

2. The identification of proteins involved in the regulation of the homeostasis of the intestinal epithelium and the regulation of intestinal barrier function. HNF-4α was identified as a regulator of epithelium homeostasis and of dietary lipid uptake. They also identified cellular prion protein PrPc in the regulation of intestinal barrier function by controlling intercellular junction of epithelial cells.

The team has been quite successful with a good record in terms of publications. 25 original publications, among them 11 originate directly from the research of the team in good journals (IF between 3.3 and 6) and one published in a journal with an IF>10 (Gastroenterology). Several of these publications are made by researchers involved in the project of the new team 4. The collaborative publications are also published in high-impact international journals (IF around 4-10) with 3 in outstanding journals (IF>10). Only one review is listed.

Former team 9 has produced interesting and original findings demonstrating the concept that the glucose transporter GLUT2 in the enterocytes is a glucose sensor in addition to its function as a transporter. This sensor function was involved in the regulation of glucose homeostasis and hypothalamic food intake. Also, interesting and original researches were performed on the role for different mutations in GLUT2 found in rare syndromes on the transporter or sensor functions. The modulation of the intracellular GLUT2 localisation by insulin in enterocytes and its alteration in insulin resistant state were also reported leading to the concept of the intestine as an insulin sensitive tissue to regulate sugar absorption. They discovered that a diet enriched in lipids increases the number of the enteroendocrine L cells (GLP-1 secreting cells) both in obese mice and humans and that this number can predict bypass surgery therapeutic success or complications.

The team has produced 12 original publications over the period, in good journals of the discipline (IF 4-9) but the number of publications coming directly from the team (5) is relatively low. There is no publication in high profile journals except for two collaborative studies with an IF>10 (Nat Genet, Gastroenterology). Two invited reviews are published in journal of IF 7.9 and 4.7 as well as 3 invited book chapters. Team members regularly attended national and international meetings and the national visibility is good. The international visibility is weak.

Assessment of the unit's academic reputation and appeal

The leader of new Team 4, the co-leader of former Team 9 and the department I scientific coordinator, has a good level of national recognition level in the field of physiology, nutrition, and glucose metabolism but she would benefit from increasing her participation at international level. New Team 4 includes researchers coming mainly from former Team 4, who obtained awards during the previous period.

Over the last period, Team 4 and former Team 9 have attracted several good students and four French post-doctoral fellows demonstrating a good reputation and appeal of the teams at national level. It would be also important to increase the attractiveness of the team at international level (as stated in SWOT).

The different members of the new team 4, including the team leader and PIs of the different subprojects, have been successful in fund-raising. However, none of the listed grants appear to be national or European collaborative/network grants, but various international and national collaborations are listed as well as collaborations with different other CRC teams. There is thus scope for increasing the participation of the new team 4 in national collaborative program (ANR) as well as in European network grant applications in order to increase its international visibility and to potentially attract researchers from abroad. The participation of the team in the IHU ICAN is certainly an added-value for the attractiveness of the team by favoring interactions with other teams of this network (over the next period, three projects have been already funded and one post-doc position has recently been obtained).

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

The team members have some limited activity in industrial transfer with 2 contracts with pharmaceutical companies and one license over the period. The team leader is consultant for a US biotech. It has been planned to reinforce the industrial valorization in the next period and the participation of the team to ICAN may help to reach this objective.

Assessment of the unit's organisation and life

The reasons to merge team 4 and former team 9 in a unique team are totally justified by the departure or retirement of researchers in both teams and by complementary expertise and complementary scientific questions in intestinal functions in health and diseases. This merging will undoubtedly allow maintaining a sufficient critical size for the future project. Even if no previous joined publications have been made, joined studies are ongoing, a strong point in favor of the creation of this new team. The planned organization has been made thoughtfully in order to really create a new team mixing members of both previous teams in the different topics, an organization which should favor a very efficient synergy between researchers. The team will be organized into three subgroups, corresponding to the major axes of the research project, each led by a senior scientist (see the detailed axis infra) citer les titres de ces axes. The size of the team seems satisfactory with a good balance of experienced and young/middle young researchers (coming from former team 4). The technical staff is presently satisfactory but two technicians will retire during the next contract. The major weakness of the organization of team is the relative low number of postdoctoral fellows and PhD students.

Assessment of the unit's involvement in training through research

Over the last period, the training activity was excellent. Several PhD students have been trained in former team 4 (8 students) and 9 (4 students). Most of them have already defended their thesis and some will defend it soon. The PhD students have published. The majority of them are in postdoc but some have a job in private companies. Members of team have also a strong activity in teaching. The proposed team leader is member of the thesis and HDR committee for life sciences of the Paris 6 University and responsible for a module at the level of Master. One member of the team had strong implication in teaching organization (director of the Physiology Physiopathology Doctoral School and of the Doctoral Training Institute, member of the pedagogic committee of the Paris 6 University, coordinator of a program for educational reform in Maghreb). Other members of the team are involved in teaching duties or pedagogic committees at different levels (master, EPHE, …..).

Assessment of the five-year plan and strategy

The general objective of the project of this team is to investigate the mechanisms of metabolic adaptations of intestinal cells to a change in nutrient flux and the pathways involved in the adaptation of intestine to obesity and diabetes.

The project will be developed along three axes:

1. The study of the integration of intestinal nutrient sensing in organism

2. The investigation of cellular mechanisms of intestinal sensing of nutrients

3. The study of epithelium structure and cell-cell junction dynamics in pathophysiology of the intestinal barrier

The originality of the new project is to investigate the role of SR-B1 and of GLUT2 in the differentiation process and function of enteroendocrine cells. The scientific question is very relevant since alterations in enteroendocrine cells secretion might contribute to metabolic disorders but how modifications of nutriment flux could impact their functions/differentiations and the mechanisms involved remain poorly understood. Another interesting aspect is the study of the structure-function of GLUT2 for the regulation of enterohormone secretions. By contrast the cellular studies proposed to investigate the mechanism involved in SR-BI-dependent enterohormone secretions seem quite limited. One aim is also to understand the link between change in gut microbiota and modifications in enteroendocrine lineage and enterohormone secretions in human (collaboration with the ICAN network) and mice. The proposed investigations will generate interesting but correlative data and without mechanistic hypothesis or studies this part of the project appears quite limited compared to the others. It is also intended to study whether ER stress affects lipid absorption and enterohormone secretions. The question is justified, even if not at the cutting-edge, since it is well-known that secretory cells often experience ER stress in different pathological conditions. The approaches to answer the questions are classical but well-defined and sound.

The third axis is potentially interesting but the scientific strategy is not very clear with some challenging approaches (analysis of autophagy in vivo in intestine) and other needs to be clarified especially concerning the gain or loss of function of autophagy regulators. The implication of desmosome proteins including PrPc as signaling platform activating different signaling pathways with consequences for barrier function and cell death/differentiation of enterocytes is an interesting and original aspect with well-justified questions able to generate data with clear fundamental and pathophysiologial outcome.

Overall, several items of the project should generate original findings with clear fundamental and clinical interest. Several tools (mice models, cell lines) as well as the established collaboration within ICAN for human studies are obviously an asset for the success of the project. However, the project will benefit from being more focussed in order to increase its chance of success. It seems also that there is some weakness in the approaches used or in the scientific strategy for some minor parts of the proposal.

Conclusion

- Strengths and opportunities:

Organization of this team should favor efficient synergy between the researchers coming from the two former teams and sharing complementary expertise and common scientific questions. The teams had recently recruited researchers with permanent positions. The strategy proposed for the new group appears sound. The attractiveness of the two teams for PhD students was very good in the past. Original questions are proposed in the project. Original models of genetically modified mice and access to clinical investigations and rare human biological samples through collaboration with the coordinator of the ICAN project are obviously an asset for the success of the project. As a whole, the project addresses important and original new aspects of intestinal cells physiology and pathology.

- Weaknesses and threats:

Weak participation in collaborative and network grant applications and no publication in outstanding journal in the past. The team leaders and the other PIs have only few invitations for plenary lecture in international meetings. The number of postdoctoral fellows (especially international ones) and perhaps PhD students is not sufficient. Weaknesses in some parts of the project concerning the strategy and/or the approaches.

- Recommendations:

The members of the team need to go from national recognition to an international visibility. Networking and funding visibility could be improved by participating to network-type grant applications with groups in other European countries, and by more participation in international societies or interest groups. Participation of this team to international networks would again increase the recognition of its work and may ease the recruitment of foreign scientists. Attention should be paid to the number of the different items in project. The project needs to be more focussed in order to remain competitive in the field.

Team 5 : Molecular Oral Pathophysiology

Name of team leader: Ms Ariane BERDAL

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	10	8	
N2: Permanent EPST or EPIC researchers and similar positions	2	2	
N3: Other permanent staff (without research duties)	8.5	7.5	
N4: Other professors (PREM, ECC, etc.)	1	1	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	3	
N6: Other contractual staff (without research duties)	0		
TOTAL N1 to N6	**23.5**	21.5	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	6	
Theses defended	16	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	10	7

• Detailed assessments

Assessment of scientific quality and outputs

Research conducted by Team 5 focusses on the tissue specificity of the oral cavity, incorporating not only the teeth but also the surrounding tissues (teeth-jaw). Oral pathophysiology is still a relatively orphan matter of research in the osteo-articular domain in France. The research conducted by Team 5 is original, quite unique, of high level in terms of molecular crosstalk investigations and genetic models. Results obtained give access to molecular diagnosis of human oral malformations and to engineered methods of reconstruction of the tooth/jaw functional apparatus. The pathophysiology of alveolar bone in particular is also compared to that of long bones in animal models. Major discoveries have been made during the last 4 years: roles of Msx1 and Msx2 with the use of sophisticated genetically modified mouse models, target matrix proteins (amelogenin, ameloblastin enamelin, DSPP) of these transcription factors (or their partners such as Dlx3) including the discovery of a new one, impact of microenvironment alteration by biomaterials on these regulations. Thanks to a new group, they obtained additional expertise in developmental biology and identified a cell subpopulation among the general population of gingival fibroblasts with potential interesting role in cell therapy, again different from cells originating from the bone marrow. They work on the concept of multi-tissue crosstalk and interdependance. It is probably the only team in France able to handle this complexity. The team has proved its ability to implement and manage theorical and methodological breakthroughs in relation with genetic models that induce major discoveries regarding the particular and complex environment characterized by the teeth-jaw tissue heterogeneity. Mouse mutation models allowed them to understand human disease phenotypes and results are linked to the creation of the Reference Centre “Rare Facial and Buccal Malformations”. The team has produced since Jan 2007, 68 original articles, 52 inside the group (2 with IF>10 ; 8 with IF between 5 and 10) and 16 in collaboration, 12 review chapters or invited commentaries. Among the Journals , BMJ open, Eur Cell Materials, J Cell Physiol, J Biol Chem, J Clin Invest, ATVC. They also published in top Journals of the field.

Assessment of the unit's academic reputation and appeal

They are active in national (9) and international (12) collaborations with joined ANR grants and often high level of publications.

The head of the team organized (or co-organized) the following meetings:

- “Tooth Enamel 8” in UK (30th anniversary, 2013 with 100-150 participants)
- 3 oral pathophysiology sessions in part with support of EuroCOST B28 in 2007, 2010 and 2011.

Two members of the team organized the “International Congress of Distraction Osteogenesis” every 3 years from 1997 (400-500 participants from all leader teams of Craniofacial Surgery in the world).

The team leader belonged to the scientific committee for the congresses “International Conference on the Chemistry and Biology of Mineralized Tissues” (Austin, Texas 2007) and “Tooth Enamel 7” (USA, 2011). Members of the team belong to the scientific committee of “Société Française des Tissus Minéralisés” (2012-14) which organizes annual meeting (100-150 participants) and organized sessions and participated to the scientific committee of the National Congress of Stomatology and Maxillo-Facial Surgery.

Two members of the team received Prices (Broken Face Foundation in 2011 and international Hans Genett’s award in 2011). The team leader has been promoted and received scientific excellence prime. Members of the team were invited as speakers in 17 international congresses and three were invited to give lectures and seminars outbroad.

The team is appealing as demontrated by the numerous post doc and for most of them, the high level of publications. The team has a national and international reputation in the treatment of facial deformities and host many visitors coming for clinical formations [15 visitors (2 months to 1 year) from 2007 to 2012: France (2), Europe (7) Africa (2) Middle East (1) Australia (1) Canada (1), Taiwann (1)]. The team coordinates a Reference Center for Rare Diseases: KRC "rare malformations of the face and cavity mouth "on which 13 national centers of competence depend.

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

The expertise of the team is within a niche and is internationally recognized.

The interactions and outpouts are:

- 7 patents (6 under license), 3 Medical devices (Stryker Leibinger and KLS Martin; Germany, CHLOC and OBL, France). 6 contracts with industry (Septodont, Maillefer, Pierre Fabre, Expanscience, ITEVA, Zimmer).

- 4 National recommendation reports (bone dysplasia and jaw osteonecrosis - three reports for AFSSaPS).

- Member and expert in 4 AFFSAPS and other committees - CPP, Ile de France and HAS organization.

- 5 participations or coordination of National Hospital Clinical Research Programs PHRC

Importantly, the Reference Centre was created to improve the erratic paths of patients affected by rare diseases due to a lack of knowledge. The production of the team is widely disseminated towards health professionals (organization of seminars, congresses), and patient associations as well public audience (4 associations of patients, 8 TV reports, Science Festival 2011, Denis Diderot tercentenary 2013).

Assessment of the unit's organisation and life

The scientific objectives of the team are well focused and the research is translationnal. The collaboration with other teams of the Centre des Cordeliers exists : Teams 3, 4 and 14 (Cell Tissues and Organs, 2009; J Cell Physiol, 2009; Molla et al., in preparation, EcosNord funding 2012-14). The unit has been remodeled substantially during the last 4 years (5 members left and 6 new comers). Despite these changes, the research program did not show any failure, hence it has been reinforced.

Regarding coordination, weekly meetings, websites, health and safety, quality and ethics, the organisation comes from the Centre, few information is given from the team itself.

The head of the team is particularly active in getting external ressources. During the past period the team also obtained 5 Bonus Quality Research (Paris 7) ; 3 Interdisciplinary University Projects (2007, 2012) ; 7 National and International foundation grants (Avenir, Broken Faces, European and International Society of Endodontics, Philipp Foundation - USA) ; 5 Academic Grants and International Exchange program (EcosNord; COFECUP application).

Assessment of the unit's involvement in training through research

The team is affiliated to GC2ID and Physiology/Physiopathology Doctoral Schools and Master Morphogenesis, Biology, Biotherapies and Biomineralization "MB3" in the Mention Cell Biology and Pathophysiology - PRES Sorbonne-Paris-City).

The team has 6 HDR and is involved in teaching at LMD and post-graduate levels.

Team members are heavily implicated in medical, dental or in biology LMD courses and training in scientific societies. Their content is able to attract students from many countries and relied to co-supervised theses in Belgium, Canada, Lebanon, UK and USA (5), Colombia (University of Antioquia), Venezuela (Creation of a Master degree financed by Ecos-Nord program) and Tunisia (PHRC TEIOS).

Three Master 1-level teaching units (18 ECTS), an International University degree which associates clinical specialization and research and a professional Master specialty leaded including tow paths including Rare Oral Diseases were created.

Assessment of the five-year plan and strategy

The project continues previous research and builds upon promising preliminary data achieved in the previous contract. The aims of the project are interdependent and translational by essence combining experimental cell, animal models and diagnosis and treatment follow-up of human rare diseases along with sophisticated method of quality/structure analysis of hard tissues.

It is built on solid foundations and remains focused on tooth and jaw deformities as models for pathophysiology linked to Msx2. Four main interrelated axes are planned, still associating animal models and clinical cases, from therapeutic exploration of neuroectodermal gingival cells from human origin to a human clinical study of maxillary bone pre-implant reconstruction (AFFSAPS requirements, CIC involvement). The cell therapy center will also store the gingival cells of patients from the Reference Center (cells carrying identified mutations will be valuable tools to analyze pathophysiology of the different cell-types). The tissue engineering theme is organized with already known industrial partners. The leader team appeared to be the best dedicated person to organize the synergy between dental teams of the Paris region (Creation of PRES Sorbonne-Paris-Cité dental school).

Conclusion

- Strengths and opportunities:

The production of the team is of high quality both in terms of publications, patents and medical devices. Most of the university/hospital team members have a good scientific production. The team leader is conducting a linear scientific strategy with pertinent scientific questions, requiring high technologies and leading to clinical applications and understanding. The creation of the reference centre “rare facial and buccal malformations” has to be highlighted. The ability to succeed in getting external resources has also to be mentioned here.

The overall project is credible. The risks seem to be measured since there are already strong scientific basis, selected industrial, clinical and scientific partners having good synergy and common objectives. The relationship and interdependency between basic and applied, clinical research are reinforced as compared to the previous contract. The networking within the team appeared optimized – despite staff movements - by using for common goals the ability of academic researchers and physicians.

There are collaboration networks both at national and international levels and good visibility of the team in the rare diseases of facial deformities.

All this constitutes strength: since this project is unique, it will not only improve the knowledge on rare diseases but also on the effects of some environmental chemical hazards. It will also serve everyday dental practice.

- Weaknesses and threats:

As underlined by the authors themselves, weaknesses are related to the lack of full time scientists, and the complexity of Paris dental schools (this may be improved in the coming years).

Threats are related to the difficulties in expanding this discipline. This is time and energy consuming maybe at the expense of other activities.

- Recommendations:

The committee suggested that it should be wise to build closer connections with other teams in the Cordeliers center working on nutrition defects and associated diseases (diabetes), since they declare to be interested in the effects of nutrition. This should be viewed as an opportunity.

Continue to provide comprehensive scheme of specificity and complexity of the multi-tissue regional jaw through investigation of signaling cascades (Msx2 and dental proteins of interest), cellular activities and links with biomaterials.

Continue transversal research from bench to clinic and vice versa (importance of rare diseases and bioengineering).

Integrate the jaw pathophysiology in metabolic challenges such as those driven by nutritional disorders (to set up more collaborations within the Center).

Encourage university/hospital team members who did not have the HDR to get it.

Encourage the institution to help the team in the participation of Paris dental schools organisation.

Team 6 : Epigenetic and environment regulation of complex phenotypes

Name of team leader: Mr Dominique GAUGUIER

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			
N2: Permanent EPST or EPIC researchers and similar positions	2	2	
N3: Other permanent staff (without research duties)	2	1	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	3	
N6: Other contractual staff (without research duties)	1	1	
TOTAL N1 to N6	**9**	**7**	

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

• Detailed assessments

Assessment of scientific quality and outputs

This is a small group created de novo three years ago (Nov 2009) by a newly recruited DR2 (INSERM) who has gained a solid experience in mammalian genetics in the UK (he was Professor of Mammalian Genetics at the University of Oxford). The group progressively increased to its actual size (1 CR1 joined the team in Dec 2011 and 2 INSERM engineers in Nov 2010 and March 2012, respectively). There are also 4 post-docs, 1 PhD student and 1 contractual technician in the group. The team is now in a better position to address its promising and challenging research programme.

Since 2007, the team has been extremely productive, since it has published 65 original articles (6 with IF > 10, 20 with IF between 5 and 10), including articles in Nature Genetics, Genome Research, PNAS, Diabetes, Diabetologia, Journal of Proteome Research, and 9 reviews (1 in Nature Genetics). This is an extremely high production given the move from Oxford during this period and the difficulties to implement a new group starting with only 2 post-docs. Of course, the head of the team participates in several international networks and many of these articles are collaborative papers. Nevertheless, he is the last author on the papers published in 2007 in Nature Genetics, Diabetologia and PNAS, and again on the latest papers published in the Journal of Proteome Research in 2011 and 2012.

The approaches are original and multidisciplinary (combining physiology, functional genomics - transcriptomics and metabolomics, genetic polymorphism data and bioinformatics methods in rat and mouse experimental models) and to several new concepts, particularly regarding the cross-talk between the composition and function of the gut microbiome and metabolic processes controlled by the host genome. The team was the first to demonstrate the successful application of metabolomics in the chromosomal mapping of quantitative metabolic variables in a mammalian species. They also showed that the genetic control of the abundance of the gut microbiota derived metabolites can be mapped to the genome, thus highlighting the effects of genetic polymorphisms on these transgenomic regulations.

Assessment of the unit's academic reputation and appeal

The team has a strong international visibility with numerous external collaborations in the fields of functional genomics, bioinformatics, and clinical genetics.

The team participated/currently participates in several networks funded by the EU (EURATOOLS, EURATRANS, METACARDIS, FGENTCARD) and coordinates the last one. The team also has a leader role in the metaanalysis of 34 genetic studies of human CMD (CardiogramPlus). The team leader has an excellent capacity to rise funding (> 2 800 000 € since 2007).

With its European partners, the team has contributed very significantly to the improvement of genetic and genomic resources for the rat.

Members of the team were invited speakers in 6 international conferences, including the Cold Spring Harbor/Wellcome Trust meeting on Rat Genomics.

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

The team has not been involved in the deposit of patents during the last 5 year-period but is an active member of the Institute of Cardiometabolism and Nutrition, which is important for future translational aspects of the research carried out in rodent models.

Assessment of the unit's organisation and life

The team will address the role of epigenetic factors and the gut microbiome on CMD phenotypes in two well-structured and interdependent axes of research. Data and expertise are being shared between team members. The team is small, and these criteria do not apply to such a small team.

Assessment of the team's involvement in training through research

The team is affiliated to the doctoral school in physiology and nutrition (Paris 6). Since 2009, the group hosted 1 PhD student and 5 post-docs, including a Marie Curie post-doc fellow funded by the EC. The team leader is conscious that the current size of the group does not allow him to supervise more PhD students and that he must attract new more experienced collaborators before he can increase his training activities.

Assessment of the five-year plan and strategy

The research project is built on strong preliminary data obtained in the laboratory with rat models and addresses novel concepts in the etiology of CMD. It relies on techniques that are familiar to the team (physiology, genomic, genetic, transcriptomic and metabolomic studies in rat strains) or that they have contributed to implement (NGS) and resources they have accumulated over the past 4 years (genetic crosses and congenic strains). The research programme combines fundamental projects and translational applications in humans.

GWAS of diabetes and obesity have identified numerous susceptibility genes which collectively only explain a small fraction of the inherited disease risk. There is evidence for a strong impact of environmental factors on the CMD "epidemics". Investigations of the intestinal microbiome and epigenetic factors are therefore particularly relevant to genes by environment interactions influencing metabolic and cardiovascular traits.

Funding is already secured for 2 post-docs starting in January 2013.

Conclusion

- Strengths and opportunities:

Research into the causes of diabetes and obesity is a central issue in medicine.

The team is actively involved in many international genetic and genomic initiatives and is aware of technological progress. This allows the team to share expertise with other groups and remain at the forefront of genomic research.

The team possesses a strong expertise in physiology and genomics.

Genetic investigations in animal models (mice and rats maintained in the laboratory) amenable to controlled experimental conditions either impossible or unethical in humans.

Translational aspects of the research programme in human genetics (involvement in the IHU ICAN) are added values that will maximize the output of results from experiments in models.

Already substantial funding is obtained to carry out the proposed research.

- Weaknesses and threats:

The size of the team is still modest to achieve all the objectives listed in the project. However, the team leader has demonstrated, when he was in Oxford (for over 15 years), his capacity to operate a larger group and the team will probably increase in size in the coming years, now that its implementation at the CRC is consolidated.

- Recommendations:

Financial resources are already secured to renew the contracts of contractual staff, particularly the post-docs, but these should be encouraged to postulate for permanent scientist positions, as this would help maintaining the leadership of the group within its scientific community. The team leader should also try to attract tenured young researchers with complementary expertise to reinforce the group more rapidly.

Team 7 : Cellular and clinical pathogenesis of diabetes

Name of team leader: Ms Fabienne FOUFELLE

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	5	
N2: Permanent EPST or EPIC researchers and similar positions	5	3	
N3: Other permanent staff (without research duties)	5	3	
N4: Other professors (PREM, ECC, etc.)	0	0	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	4	
N6: Other contractual staff (without research duties)	4	3	
TOTAL N1 to N6	**20**	**18**	

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	3	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	8	6

• Detailed assessments

Assessment of scientific quality and outputs

The activity of this large team is focused on the study of the physiopathology of obesity and type 2 diabetes. This is in an internationally highly competitive area and the team has made original contributions in the field by using original animal models and cellular approaches. The team has developed a project along three scientific axes in order to identify:

1. The cellular and molecular mechanisms involved in the development of hepatic steatosis and lipid-induced insulin resistance. They uncovered the implication of ER stress as an important mechanism driving liver lipogenesis in insulin resistant states. It is an important contribution to better understand why lipogenesis is very active in the liver of obese rodents despite hepatic insulin resistance. They also showed that lipid-induced ER stress is not sufficient to promote muscle insulin resistance suggesting that ER stress activation is not always linked to an alteration of insulin resistance and that the level of ER stress should be taken into consideration.

2. The regulation of lipid storage in adipocytes focusing on the biology of lipid droplets. Original findings were produced about the role of caveolin-1 in adipocytes in the regulation of lipid droplet expandability, lipid storage and fat cell function and a null-mutation in caveolin-1 was identified in congenital lipodystrophy. They provide new data suggesting that autophagy could be responsible for the lipoatrophic phenotype at least in mice.

3. The role of fetal programming in the development of type 2 diabetes. Glucorticoids were identified as major actors of the fetal programming of beta cell dysfunction and PGC-1α was demonstrated as an important actor in the regulation of beta-cell mass and function by GC.

The output of this research is excellent. The group was very productive with 51 original articles and 22 reviews from 2007-2012. Among the original articles, 22 originated from the research of the group (J Clin Invest, Cell metabolism, MCB, PNAS). The others are from collaborations with different national or international groups which highlighted the visibility of the team. The articles were generally published in high-impact international journals (IF around 5-10) but the team also published in outstanding journals with 3 publications (two from the team JCI, PNAS and one in collaboration Cell metabolism) in journals with an IF>10. Reviews are also published in high-impact international journals (Curr opin lipidol, Trends Mol Med).

Assessment of the unit's academic reputation and appeal

The team has a leading position in its research field with an excellent track record and a very good national and international visibility. Team members attended many international meetings and regularly gave invited talks (111 invitations: 32 international and 79 national).

The team has a very solid track record. The present and the future team leaders as well as the different PIs responsible for the different sub-projects are well-known in the field, regularly participating in, or invited to, European and international conferences. Several participations in national or international evaluation committees are listed. The team has developed several national and international collaborations as well as collaborations with other teams in the Centre. The team attracts several good students and French post-doctoral fellows. It would be important to attract also researchers from abroad. Visiting scientists have been welcomed for different periods of time.

The team has been very successful in fund-raising, with external research income of 4.6M € during the previous period and with different team members involved in national and international grants as PI or participant including national and European collaborative/network grants (4 EU grants as participant and 4 ANR grants for the period). The clinical research is very well funded with numerous clinical grants (PHRC and Translational Clinical Research grant). Perhaps the only scope for improvement might be to coordinate EU network or more national network grants in the future.

The team is member of the IHU ICAN “Institute of Cardiometabolism and Nutrition” a network of 14 research teams. This participation in ICAN project should strengthen translational programs of the team and favor collaborative fundamental and preclinical projects.

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

The team has had five industrial contracts with pharmaceutical companies over the period. The present and future team leaders are involved in scientific committees of international food industry and French biotechnology. No patent listed. The scientific project of the team has the potential to identify new patentable targets and more activities in this area would be desirable.

The team has developed clinical links and clinicians are members of the team and have strong research interests (as an example, a PU-PH leads the topic on fetal programming). Several translational studies were initiated in order to extend in humans the findings found in the different topics of the project. The future Team leader has an interface contract with hospital.

Assessment of the unit's organisation and life

Organization and recruitment in this team appear excellent and productive. Over the previous period, the team was organized in three subgroups. For the next contract, the team will be reorganized into two subgroups because the PI and members of the adipocyte subgroup have left. One subgroup, headed by the proposed team leader, will study lipid metabolism and insulin resistance; the other one will study the origin and mechanisms of β–cell dysfunction during fetal programming. Compared to the previous period, the β-cell subgroup will be reinforced by the arrival of an Assistant Professor and senior scientist who have an expertise in the development of pancreas. The β–cell subgroup will be co-leaded by the PU-PH and the Assistant Professor. Three postdoc and two PhD students are in the staff with 5 engineers or technicians (among them two have short-term contract).

The present team leader is the proposed director of the Centre for the next term and the future team leader is an excellent investigator who has made major contributions in the understanding of the development of hepatic steatosis. She has a strong publication records, publishing in high-impact international journals. National and international visibility is excellent. She was successful to raise funds at local, national and European granting institutions (2 EU grants, 4 ANR grants, 1 CORDIM, 1 PHRC, 3 industrial contracts over the next period). The new team organization appears well sounded, although there is a slight imbalance between the two axes with axis one stronger than axis two in term of staff members. The team is adequately structured with a good balance of experienced researchers and clinicians. However, the recruitment of one more PhD and of young full time researchers (especially for the beta-cells topic) should be considered in the future.

Assessment of the unit's involvement in training through research

Over the last period, the training activity was excellent. Six PhD students defended their thesis and have published during the period and two PhD students started their thesis in October 2012. One of the PhD obtained an award in 2009 for the quality of her thesis. One PhD student has been recruited Assistant Professor in the team. The other 4 are in postdoc.

The team members have teaching activities and are implicated in the organization of the teaching. The present team leader is head of the teaching department of Biochemistry and Molecular biology at the UPMC medical faculty. The present and future team leaders are members of the Scientific Council of the Doctoral School. The different members of the team are involved in teaching at different levels.

Assessment of the five-year plan and strategy

The project is divided in two axes focusing on the two major causes of type 2 diabetes: insulin resistance and beta cell failure.

The first axis deals with the characterization of the mechanisms involved in hepatic and skeletal muscle insulin resistance. Future proposed extensions of the effect of ER stress on SREBP-1c and lipogenesis activation as well as the study on the role of branch chain amino acids and mTOR pathway on these processes seem strong and competitive. The proposed area of the role of SREBP-1a in Kuppfer cells for the development of liver inflammation and steatosis is well justified and based on a recent report on the role of this protein in macrophages. A clinical study aiming at addressing the physiopathology of the complex interactions between liver steatosis and type 2 diabetes will benefit from the close collaboration with the diabetology unit of the St Louis Hospital. Another aim is to explore the potential of lowering ceramide concentrations to treat skeletal muscle insulin resistance. The strategy is well described and perfectly justified going from the identification of toxic ceramide species to the inhibition of their synthesis or to the speeding-up of their metabolism in non-toxic lipid species.

The second axis deals with implication of the fetal programming and infection in type 2 diabetes. The first aim is to pursue the investigation by which glucocorticoid and PGC-1alpha regulate beta-cell mass and function. The study of mice that overexpress PGC-alpha in beta-cell and the study of epigenetic modifications induced by nutrients and GC will be performed. The different studies are potentially interesting but care should be taken especially for the epigenetic topic since it is in a highly competitive area with several other strong groups already at work. The team should perhaps find a "niche" to remain competitive. Team leader is aware of that and believes that GC studies could be a valuable "niche" in the field. The aim 2 proposes different clinical studies in order to investigate fetal programming due to hyperglycemic or high glucocorticoid conditions during pregnancy and to pursue the investigation of the relationship between herpes virus type 8 infections and ketosis prone type 2 diabetes. This latter theme perhaps appears a little far away from the main interests of the group. There is also perhaps a scope for collaboration with team 2 to study the impact of hyperglycemia on the epigenetic modifications in the off-springs.

Overall, the proposal seems generally carefully designed, feasible and worthwhile, stemming from the complementary expertise of the different members of the team. The different objectives are clearly justified and the experimental strategy seems adequate combining cellular studies, genetically modified animals and translational studies in diabetic patients. Some parts of the project are the continuation of the results obtained in the past few years but original and promising new axes are also proposed. However, care should be taken for the fetal programming part of the project in order to be competitive in this field. The announced major objectives can be attained in the next 5 years if attention is paid to the number of developed projects in order to remain competitive in a highly competitive field.

Conclusion

- Strengths and opportunities:

It is an excellent team which has generated important advances in the field of hepatic steatosis and insulin resistance. Excellent track record; very productive for publications with some publications in outstanding journals; impressive ability to raise funds, European and international reputation. Participation in collaborations and scientific societies. Complementary expertise of the different members of the team. The change in team leader for the next period should not modify the scientific output of the team since the future team leader has a very good track record for publications, invitation and funding. Overall the project proposal is generally carefully designed and interesting. The cooperation between clinicians and scientists favors the translational studies.

- Weaknesses and threats:

There is scope for more international recruitment of postdoc or PhD students through international programs and for coordination of EU networks or more national networks. The team has the capacity to increase the number of publications in outstanding journal. A relative weakness in the industrial valorisation with no patents but industrial contracts. A relative weakness in the synergy between the two themes of the group.

- Recommendations:

Recruitment of one more PhD and of young full time researchers, specially to reinforce the theme 2 should be considered in the future to remain competitive in this area. In the same way, the team should find a "niche", especially in the epigenetic field to be competitive in this area. The synergy between the two themes could be reinforced by common scientific questions. The scientific project of the team as the potential to identify new patentable targets and more activity in this area is thus possible.

Team 8 : Complement and Diseases

Name of team leader: Ms Véronique FREMEAUX-BACCHI

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	
N2: Permanent EPST or EPIC researchers and similar positions		1	
N3: Other permanent staff (without research duties)		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)			
TOTAL N1 to N6		**4**	

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

• Detailed assessments

Assessment of scientific quality and outputs

The team is created an an independent group dedicated to complement research in the project. It was previously included in a subgroup of another team. The capacity to link biochemical/genetic work with clinical observations is unique. The output of high quality papers in the top nephrology and haematology journals attest for it. Major novelties were in the discovery of anti-Factor H autoantibodies, hyper-functional C3 in the atypical Hemolytic Uremic Syndrome (aHUS), the relation between complement abnormalities and C3 nephritis, and recently the finding of a C1q mutation leading to reduced capacity to react with C1rs in an Systemic Lupus Erythematosus patient. All these original findings have been obtained in recent years, including 2012. The group is of a small size, and produced some excellent publications (Blood 2009, 2012, J Immunology, Kidney international...). The recent increase in publications was mainly due to clinical collaborations and reviews. The publications of the group were presented at major international congresses, under expert scrutiny, and it is worthwhile to say that the data presented were well presented and novel.

It would be fine for the group to delegate reviews in French to external collaborators.

Assessment of the unit's academic reputation and appeal

The group belongs to the worldwide top complement research groups. The team leader is a leading member of international societies in that field. She is highly regarded, mainly because the work done in Paris is well done and relates complement to diseases, particularly kidney diseases.

Complement like many biological fields is complex, has complex interactions with other systems and is relevant in many diseases (infections, autoimmunity, cancer, etc). Internationally the appeal for doing “complement research” has been low for the last 20 years, since most of the proteins and genes had been discovered at that time. However, this is changing thanks the contribution of genetics (also from the group), since different diseases are now again linked more specifically to complement gene defects. The possibility to block complement (antiC5 Ab) had also a major impact for clinicians, who want to know more about complement.

Thus, the team will have the advantage to be able to recruit young researchers, mainly French clinicians who want to have basic knowledge in the field, but also basic researchers coming from eastern countries (one such recent addition was excellent), where the interest to do research is still extremely high. The difficulty for all French research groups is to be internationally attractive for scientists who speak English but not French.

The team leader is in the best position to organize international complement meetings, what she should do. This might help recruitment as well.

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

The interaction with clinicians in France (and Switzerland at least) is perfect. The input at science meetings is of highest value. The group is internationally integrated in a network of excellence.

The findings of the group have modified clinical practice for many patients (finding mutations, counseling families).

The relation with economy has been low for the group until recently – when the collaboration with Alexion started (the company producing the antiC5 Ab) including clinical trials. Here, the team leader is at the forefront of clinical research, not only nationally but also internationally (collaborative clinical work on antiC5 in HUS, letter in the NEJM, and on transplantation of aHUS).

Assessment of the unit's organisation and life

The unit is very well structured with each member having a specific and unique function, although clearly working together. The teaching options appear to be limited.

Assessment of the unit's involvement in training through research

From the written documents: fine, the members appear to progress from the time they initiated as an independent group.

Assessment of the five-year plan and strategy

There is a fine balance between low and high risk projects, and between basic biochemistry, genetics and clinical correlations. Impressive, perhaps overambitious, but globally excellent, in particular because it takes advantages of local and international collaborations. The team leader is known to be hard working and making sure that collaborations work. A difficulty is to propose work for 5 years, knowing that research projects are constantly influenced by novel findings (and rightly so).

The first objective is to define the relation between complement activation and cell damage in different organs. Interactions with the coagulation cascade are central, which is very logical and has to date not been explored properly. The toxic effect of complement on cells, and/ or the modifications induced by complement will be explored as well. Here the aim at looking at different endothelial cells is well taken, it might be more difficult to correlate data of cell cultures with the *in vivo* situation of endothelial cells. The mesangial cells are certainly other targets of complement and the projected studies trying to link *in vitro* data with biopsies is an interesting step towards trying to elucidate the glomerular damage in C3 nephritis. It might have been interesting to discuss the role of podocytes in glomerular injury in relation to complement.

The emergence of auto-antibodies responsible for the deregulation of complement has not been understood, neither to which epitopes these antibodies are directed. The approach of the team is broad, feasible and is likely to bring new information to the field.

The recent work on C1q has evidently given new ideas to the team: "C1q and apoptosis revisited" could be her title; to define the exact molecular interactions between C1q and the apoptotic cell thanks to the knowledge gained over recent years. This is refreshing and relevant to autoimmunity.

These comments should be put into the context of an excellent global approach of complement with cell damage and damaged cells. The team leader has the advantage to be a perfect biochemist and a physician who understands the clinical correlations. She is the perfect translational researcher.

Conclusion

- Strengths and opportunities:

Powerful leader, small team with internally direct interactions, reacting rapidly to novelties, taking advantage of their own strength, but also collaborating with French and European clinicians and internationally, innovative. Novel projects going beyond what has been done until now. They will be able to collaborate in clinical trials with companies developing anti-complement products.

- Weaknesses and threats:

Many new projects going into different directions, with -to date – no complete technical knowledge (this last comment should however be dampened since a recent collaboration is a real advantage).

Remaining in the field of rare diseases.

Hurdles associated with securing funding for a niche type of research.

- Recommendations:

The group became rightly autonomous: this should be further supported.

To encourage some members of the team to apply for promotion or tenured position.

Autonomy should not mean "put on the side". Integration in teaching should be favoured: many aspects could be integrated as examples of genetics, biochemistry and translational research.

Recruitment should be improved (looking outside France, organizing meetings, emphasizing the type of work done: cell and molecular biology – not just "complement", because this is for many young scientist at the start of their career more importance than the specific work.

Team 9 : Apoptosis, Cancer & Immunity

Name of team leader: Mr Guido KROEMER

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	
N2: Permanent EPST or EPIC researchers and similar positions	5	5	
N3: Other permanent staff (without research duties)	3	6	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	12	10	
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**22**	**22**	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	15	
Theses defended	9	
Postdoctoral students having spent at least 12 months in the unit	12	
Number of Research Supervisor Qualifications (HDR) taken	Not indicated	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

Mr Guido KROEMER's team will join the CRC in 2013. Part of his team will remain located at Institute Gustave Roussy (IGR). Thus this evaluation concerns the 5 past years at IGR (INSERM U848).

The scientific achievements of the team are outstanding. Over the past 5 years the team has made several key contributions to our understanding of the role of mitochondria in apoptosis, of autophagy and its role in longevity, and how mitotic catastrophe can contribute to malignant transformation. In addition the group has continued to develop the work based on the concept of immunogenic cell death and identified a number of events that appear to be required for the immunogenicity of tumoral cells. All this work has been published in 206 articles (65 with IF > 10). In addition, the team has produced 94 reviews (36 with IF> 10).

Assessment of the unit's academic reputation and appeal

The team leader is a well recognized world leader who has made essential contributions in the field of cell death and autophagy. He has been invited to participate in 127 international conferences and on many occasions gave keynote lectures. He also organized multiple international conferences and received numerous prizes. He has also many other activities that keep him extremely busy (for example: director of the Paris Alliance of Cancer Research Institutes; director of the LabEx Immunology-Oncology; member of several academies, editor, or member of the editorial board, of several journals). He is probably one of the best known scientists in the world.

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

The team leader has established several contracts with industrial partners, collaborates with the Insurance company AXA, and participates in 5 international grants provided by the European Union.

Assessment of the unit's organisation and life

The team is composed of senior scientists (4CR1, 3 at INSERM, 1 at CNRS, and 1 CR2 INSERM) and a PUPH (université Paris 13), 12 post-docs, 15 PhDs and 2 IE and 1 AI.

Assessment of the unit's involvement in training through research

The team is affiliated to the Doctoral School in Cancerology of University Paris, IGR. Currently 15 PhD students are in the team and are supervised by 4 scientists entitled to direct PhD research programs (HDR). 1-3 Master students per year.

Assessment of the five-year plan and strategy

The main objective of the team is to understand the mechanisms of immunogenic cell death. The goal is to render cells more immunogenic. The team will continue to explore the role of premortem stresses such as ER stress and calreticulin exposure, autophagy and ATP release and finally the release of HMGB1 in immunogenic cell death. If the importance of these stresses is confirmed, then anticancer drugs that favor their apparition may be useful in eliciting anticancer immune responses.

The team will also look for predictive biomarkers (hallmarks of autophagy for example). Here a close collaboration with Team 12 may prove to be fruitful.

All this work may lead to the design of anticancer vaccines in the form of dead cells exposing some of the key immunogenic stresses.

In addition, the group will be involved in preventing various forms of cell death occuring in neurodegenerative diseases.

Overall this is a very ambitious project proposed by a team that has all the expertise either in house, or through the impressive number of already established collaborations. All the proposed projects are feasible and may lead to scientific breakthrough in the field of cancer therapy.

Conclusion

● Strengths and opportunities:

World-class expertise in the different types of programmed cell death and autophagy. The team leader is a major international figure in science.

Positioning both nationally and internationally as a leading group in cancer immunology and its connections with cell biological processes.

A dense network of collaborations with major teams both in France and abroad.

A diversified portfolio of grants and funding for a good critical mass of researchers.

High technology platforms built by the team (metabolomics, robotized fluorescence videomicroscopy, high throughput/high content analysis screening capabilities).

● Weaknesses and recommendations:

The research program is ambitious and overreaching, therefore with a certain dose of high risk taking.

The team leader is in high demand and committed to leading numerous excellence networks and academic/scholar activities.

The publication record is of such caliber and quality that it may not be necessary to “dilute” it with numerous reviews of apparently redundant content.

The animal facilities should be strenghtened.

The opportunities for a full and productive integration of the team to the CRC should be exploited on the occasion of the deployment of the team at the CRC facilities this coming summer.

Team 10 : Bacterial structures involved in antibiotic resistance modulation

Name of team leader: Mr Michel ARTHUR

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	4	
N2: Permanent EPST or EPIC researchers and similar positions	1	1	
N3: Other permanent staff (without research duties)	3	3	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1	
N6: Other contractual staff (without research duties)	1		
TOTAL N1 to N6	**10**	**9**	

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	3	
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 central scope of the team is the elucidation of the synthesis, the organization, the remodeling of the peptidoglycans (PG). More specifically, the team is focused on a particular aspect of PG synthesis, i.e. its cross-linking, a key process leading to the structural organization of this vital component of the bacterial wall. The study of these aspects is essential for various reasons. The most obvious one is the fact that the cross linking of cell wall PG is the target of the betalactams which remain the most broadly used drugs globally. In a fundamental point of view, the biosynthetic mechanisms of this complex pathway remain largely uncovered. The team objectives are clearly to gain insight on the fine tune synthetic steps of the PG, which should help:

1. to better understand the mechanism of resistance developed by bacteria against beta-lactams.
2. to identify key process that are not yet exploited by modern antibiotherapy.
3. ultimately, to develop new compounds to fight natural or acquired resistance to beta-lactams.

The team is certainly one of the most gifted in Europe to approach these complex questions. The team is composed of scientists with a long and highly complementary expertise to address the problem with the needed global perspective. The core team is indeed rich of 3 worldwide renowned experts with a long experience in fundamental and clinical microbiology, biochemistry, molecular genetics, with strong interaction with the hospital. The team permanently confronts the daily problems of bacterial resistance at the clinical level with the various strategies that emerge from the results generated in the laboratory. These are probably the most appropriate conditions to see the emergence of novel concepts adapted to the current clinical needs.

In its quest of knowledge to design new therapeutic perspectives, the team has made outstanding progresses:

1. the identification of a cryptic locus controlling the activation of the L,D-transpeptidation which partially explains cross-resistance mechanisms to beta-lactams and glycopeptides.
2. essential contributions to the understanding of the specificity of PG cross-linking enzymes.
3. development of inhibition assays of Fem enzymes that are in charge of the synthesis of the side chain of peptidoglycan precursors.
4. unraveling of a new mechanism of action of carbapenem, showing that action of beta-lactams is not restricted to the inhibition of D,D transpeptidase.
5. understanding the key aspects of the mode of action of carbapenem against the L,D transpeptidase of *M. tuberculosis*, which opens both immediate and future therapeutic perspectives.
6. finally, the group has started to explore partners of transpeptidases, which may also help to understand some resistance mechanisms, and eventually lead to identify new therapeutic targets.

To gain insight in the different questions the laboratory has used an impressive panel of techniques. Most of biochemical, molecular biology, and microbiology techniques are performed by the team, including innovative fluorescence based methodology, but when necessary the team has required specific collaborations such as for the elucidation of protein structures by NMR (CNRS Grenoble1), chemical synthesis or semi-synthesis of inhibitors or substrates (UMR7201, UMR8610), evaluation of antituberculosis compound activity (CNR-mycobacteries).

Since 2007, the team, composed of 6 permanent scientists (3.5 ETP), 6 postdocs, 3 PhD 3 ITA, has published 34 original articles specifically focused on the topics discussed here, and, independently, 35 additional articles focused on the clinical activities of the members. Out of the 34 original papers, 14 were published in journals with IF > 5, including two with IF >10 (Nat Med, Angew Chem Int Ed Engl)r). The strong cross-interdisciplinarity at the chemistry-biology interface is one of the strength of the team (6 papers published at the interface).

Assessment of the unit's academic reputation and appeal

The reputation of the team is internationnaly recognized due to the high, constant, and indisputable quality of the work. There is no doubt that the recent results of the team will eventually endup in textbooks treating of bacterial enveloppe.

The national and international outlook of the team also translates in an impressively successful collect of grants, not only from France (1 FRM, 4 ANR, Palumed), but also from EU (FP6, FP7), Industry (Pierre Fabre), foundations and notably, 2 grants from the NIH. The amount collected since 2004 is 2,6 million €.

The team has trained 9 PhD students since 2007. One student has started his PhD in 2012 and one will start in 2013. During the same period, 9 master students have been trained. Six postdocs worked in the team during the last 5 years, supported by National (ANR, FRM), European (FP6), and US (NIH) grants. Three new postdocs will be supported in 2013 by ANR, FP7 and the NIH. The lab has also supported the salary of an AI for 2 years (ANR). One visitor scientist specialized in PG ligase and in drug discovery in this field has been hosted for 3 month during the past contract.

The 3 Senior scientists of the lab have been invited in renowned International Symposium as chairs or invited speakers. MA (Portugal, [Invited speaker] ICAAC [chair and speaker] UKCan meeting). PI's and young investigators have been invited to give a Keynote lecture at ECCMID 2012, in the BacWAN meeting, Gordon Research TB Conference 2010 in Oxford. One PI represents the French party for the Joint Programming on Antimicrobial Resistance at the EU. Globally, members of the team have been invited as speakers in 22 French congresses.

The Team leader is also member of the editorial board of 2 renowned international journals (Antimicrob Agents Chemother, Microbial Drug Resistance) and is active in many national and international grants and laboratory reviewing committees including ANR and AERES (3 times, including 2 times as president). One PI is Associated Editor of Clin Microbiol Infect and is an expert for PHRC evaluation.

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

Since 2007, members of the team have been involved in the deposit of 3 patents related to the field of antibiotherapy. Four articles have been written in books and one written communication was made in Med Sci for a broad audience. The team has participated to scientific debate through 4 editorials and /or comments which confirm its strong influence and implication in the field of antibiotherapy in general and b-lactams in particular.

Assessment of the unit's organisation and life

As mentioned earlier, the team is highly focused on the important question of the mechanism of action of b-lactamin and the mechanism of its associated resistance. This scientific objective, whereas sufficiently specialized, but of crucial importance, gives to the unit a clear visibility towards the scientific community. The objective is however sufficiently large to give to all PI's of the team a specific question to address without competing internally.

Based on its SWOT analysis, the team is perfectly conscious of the necessity to collaborate with specialized partners to enrich its subjects and make them innovative multidisciplinary research projects. For that, the team has established strong and stable collaboration with complementary groups and this strategy should be encouraged. As mentioned by its director, whereas more multidisciplinarity projects are immediate intentions of the group, more financial support, difficult to find, are needed to progress in this direction.

There are limited resources present in the CRC structure that would be of direct interest for this team, which would be more interested by physicochemistry, synthetic chemistry, pharmacology expertises. It is difficult to evaluate whether a direct geographical proximity of these resources would be beneficial. The group is anyway at geographical proximity with many specialized teams in Paris. It is also important to notice that connections with specialized disciplines at a certain time may rapidly change with the evolution of the project or with the rapid evolution of new techniques.

Assessment of the five-year plan and strategy

The long-term objective of the team is to continue its quest in the comprehension of the catalytic mechanism underlying PG cross-linking reactions, and to develop therapeutic tools that may emerge from this research.

The 4 main research lines presented in the progress report have been maintained in the project. This decision seems logical as each project was successful in the previous period.

In terms of manpower, these 4 projects will be managed by 3 PI's, for "Mycobacterial L,D-transpeptidases", for "In vitro inactivation of L,D-transpeptidases", and for "Activation of L,D-transpeptidation pathways and FEM transferases". Each PI will be "teamed" in its task with minimum 1 Full time equivalent Scientist, 1 ITA, and 2 postdocs. This sounds a fairly well equilibrated choice to give each PI and project the necessary manpower to succeed in its task.

The risk associated to each project is probably limited as 1) projects are built on strong data acquired during the last period, 2) they contain various aspects, which allow for choices during the scientific progression and permit possible "no-goes", 3) they will be led by experienced PIs, but still in direct connection to the sphere of competence of the other PIs of the lab, which preclude to technical or conceptual autarchy. 4) the team leader is well aware that projects will high value exist mainly through multidisciplinarity. Then, finding the good balance between diversification of the internal competences without diluting its own knowhow, and sufficient external collaborations without diluting its own project identity, is certainly the main challenge. Again, the SWOT analysis reveals that the team leader is perfectly aware of this challenge.

Valuable choices in translational research require good support from the clinic, in a certain proportion from the pharmaceutical world, including big pharma, and a good support also from "industrial property departments". The team has collected all this key processes. As mentioned in the SWOT analysis, there are difficulties to translate academic results to the market. It is probably easier to do so in the field of nosocomial infections than in the field of tuberculosis, for which there are limited profitable market perspectives. Two remarks may emerge from this. 1. It may be interesting to increase the efforts of finding private partners in the field of nosocomial infections, 2. It is the Institution's responsibility to decide to support innovative research on TB, independently of the immediate support of Pharma companies.

Conclusion

- Strengths and opportunities:

Strong expertise of the whole permanent team in the field corresponding to both the report and the project. This strength produces an original, convincing and highly pertinent research. The team draws up scientific questions, and then explores all needed techniques to answer it. Moreover, the team applies its expertise to different pathogens, irrespectively of the technical difficulties. This courageous choice must be encouraged as innovative observations often emerge from the comparison of analogous systems.

In conclusion, the team has all knowledge, willingness and original projects to identify either new ways of revalorizing ¤-lactam families, or new targets and inhibitors in the PG cross-linking pathways.

- Weaknesses and recommendations:

It would be indeed a serious benefit for the team to increase its manpower by recruiting one or two full time CR.

The opportunity of the participation of this team in the CRC has been questioned, and if possible, more collaborations should be established with other teams of the CRC.

In its quest of new inhibitors, the team may need to identify, in addition to its synthetic chemistry partners, pharmaceutical chemists to help them generating and analysing inhibitors with acceptable drug properties. It is indeed often very difficult to improve the biodisponibility of inhibitors that have been identified exclusively on their in vitro activity.

Team 11 : Cancers, Immune Control and Escape

Name of team leader: Ms Isabelle CREMER / Mr Jean-Luc TEILLAUD

Workforce : this team is the result of the merge of previous Team 13 and Team 14. The numbers are given as the sum of the 2 teams.

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producer
N1: Permanent professors and similar positions	7	5	
N2: Permanent EPST or EPIC researchers and similar positions	3	2	
N3: Other permanent staff (without research duties)	6	3.5	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	1	
N6: Other contractual staff (without research duties)	6		
TOTAL N1 to N6	**24**	**11.5**	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	10	
Theses defended	9	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	5	
Qualified research supervisors (with an HDR) or similar positions	9	

• Detailed assessments

Assessment of scientific quality and outputs

The past Team 13 and Team 14 have been large and important components of CRC Department II with more than 50 staff. The past Team 13 has focussed on a wide ranging and ambitious programme with 5 **major themes including:**

1) The role of TLR 7/8 on NSCLC and resistance to chemotherapy
2) The phenotype of intratumoral NK cells
3) The discovery and prognostic value of tertiary lymphoid structures in NSCLC
4) The immune Contexture in cancer
5) Genetic and acquired abnormalities in aHUS (not for consideration here)

The previous Team 13 (last 5 years) has delivered an outstanding output with 135 original articles, either exclusively from the Team or as a result of national and international collaborations, with more than 20 in top (>10 IF) Journals. They are an internationally recognised force who have helped mould our current understanding of cancer immunology, the importance of leukocyte infiltration in determining prognosis and the ability of the cancer microenvironment to modulate immune recognition through receptor inactivation. In the current programme they have moved from focusing on the acquired cancer immunity to investigate innate recognition both on the tumor (TLR7/8) and by NK cells.

Previous Team 14, although small, delivered some important work particularly showing the possibility that antibody serotherapy with anti-CD20 could promote acquired immunity in a mouse model of lymphoma. The most impressive aspect of this Team's work is its impact in translating current thinking into clinical trials as a result of its alliance with Laboratoire francais du Fractionnement et des Biotechnologies (LFB). It is not clear if this anti-CD20 work has social impact in the long term since this is a highly competitive field with more than 15 such reagents in development and two reagents approved for human use.

For the current contract a new team will be formed from a merger of parts of the Immune Microenvironment and tumor team (6.93 FTE) and the Laboratory of antibody Bio-engineering (2.83 FTE). Importantly, the Complement sub-group of previous Team 13 will form a new team (Team 8) and will not be considered here. The new team will be co-directed Ms. Isabelle CREMER and Mr Jean-Luc TEILLAUD, until 2016 when Mr Jean-Luc TEILLAUD will retire leaving Ms. Isabelle CREMER as sole Director.

Assessment of the unit's academic reputation and appeal

In addition to this scientific progress, the CRC has helped establishing cancer immunology and tumor microenvironment as a field in Europe, organising the first European Congress of Immunology (2006) with more than 5000 delegates and brought the field together with organisations such as the European Academy of Tumor Immunology. Ms. Isabelle CREMER is the Head of the Doctoral Schoold at Paris 6 university. One of the team members is an internationally solicited leader in the field and was recently awarded the prestigious W. B. Coley prize, and another one is past President of the European Federation of Immunological Societies. The team participates of multiple collaborative groups such as PACRI, SIRIC CARPEM, LABEX Immuno-Oncology, LYSA and has a robust partnership with the American biotech company MedImmune.

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

There is a general lack of website access to the site which is disappointing and is missing a major opportunity for recruiting international postdoctoral workers, PhD students and for advertising the centre as a whole.

Assessment of the unit's organisation and life

The reorganisation of the new Team appears to have been caused partly by the imminent retirement of key leaders and partly by changes in its scientific priority. While the reorganisation is logical and brings opportunity, it also introduces a degree of risk and may alter the priority of different projects.

The new team will be will be led by Ms. Isabelle CREMER and Mr Jean-Luc TEILLAUD. This appears like a reasonable fit with Ms. Isabelle CREMER's research benefiting from work on antibody and mouse models and Mr Jean-Luc TEILLAUD's team increasing in number and having access to expertise in tumor immunity and microenvironment. It will have 37 members, 13 of which tenured, 10 researchers, 8 lab technicians, 2 postdocs and 14 PhD students. The new team appears to have access to good research facilities. They appear to have good animal facilities, yet overall it is not clear that animal models are being used optimally in their research.

Assessment of the unit's involvement in training through research

The new team appears very well placed to train both PhD and Masters Students with excellent links and joint appointment with the major Universities in Paris. It is not clear that enough effort is being made to attract overseas students, but this may be done via the University Websites. The training of 14 doctoral students makes an excellent ratio to the size of the team.

Assessment of the five-year plan and strategy

The new team will develop a programme based on plasticity of the immune microenvioronment during tumor progression as well as its relationship with tumour genetics status and tissue of origin, with one of the most novel components being the role of local antibodies and B cells in regulating tumor microenvironment. While the new programme is focused around the key observations made by the old Teams 13/14, it makes use (refers to) of relatively few of the >100 articles produced in the last 5 years. The role of endogenous ligands for TLR-7 in lung cancer is one of the projects in the LABEX Immuno-Oncology. A third part of the future project will address the adaptive anti-tumor immunity triggered by antibody therapy, or vaccine effect.

The new team leader will no doubt benefit from Mr Jean-Luc TEILLAUD's experience and support to make this transition work effectively. While her high quality output appears limited, interestingly it has accelerated markedly in the last few years suggesting good future potential. Importantly she has started collaborating and publishing with world leading cancer immunologist suggesting that she will be better placed to take over as sole leader in 2016.

The programme has 3 exciting themes which focus on tumor microenvironment with a particular emphasis on innate recognition, but also an interesting aspect of tumor-associated B cells and their possible role in regulating tumor development. These themes include:

1) To investigate the characteristics and functionality of the immune infiltrate of primary tumors and metastases.

1a: To decipher the plasticity of the immune microenvironment during tumor progression and identify the drivers of the immune contexture.

1b: To study the anti-tumoral functions of innate and adaptive immune cells infiltrating primary lung tumors and lung metastasis. Mature DC, B cells and NK cells (not linked to NSCLC prognosis), particularly in Ti-BALT give good prognosis- this is very interesting and novel (especially the role of B cells and possible role of NK cells) and also suggest that local Ab production could be important. Following anti-tumor Ab in situ may be a challenging task. How to preserve function once cells are removed from tissue? NK cell (down regulation of key activation markers) and B cell studies are novel and give the Team a competitive advantage in the field.

1c: To identify the TAAs recognised by locally secreted Abs and T cells in primary and metastatic tumor. The assumption that locally produced antibody may be directed at specific antigens is high risk and chasing T-cell TAA is more convincing and could be helpful.

2) To analyse the modulation of the adaptive immune response by antibody-based therapies. Models other than the A20 may be considered (lymphoid and non-lymphoid including spontaneous tumors).

3) To examine tumor development in an inflammatory or infectious context. They will identify the pathway(s) leading to chemoresistance of TLR7+ tumors. Expression of Bcl-2 members and ABC transporters. And dissect the delicate balance of the influence of TLR7 on tumor vs immune cells which includes work in animals. Finally they will study inflammation of tumor development in COPD patients and a mouse model of COPD when it is developed.

The five-year programme appears excellent and has picked up and builds on the key findings to emerge from the last programme. There appears to be a move from looking at acquired immunity to innate immunity, which is novel and gives the team a good competitive edge. In addition it retains the interest in Ti-BALT and B cells which develop in NSCLC.

Conclusion

- Strengths and opportunities:

The strength of the team has grown from the previous leadership and the insights made into cancer immunology and tumor microenvironment. It also comes from the developments in the field which happily have coincided with the current programme. This timing brings strength and opportunity as interest from around the world grows. This is seen from the increase in attendance at cancer immunotherapy conferences in the last decade. The CRC, including this team, is ideally placed to take advantage.

This team has identified a list of ways to raise their international profile and secure more overseas applications. This is a great opportunity to build on their strength and reputation. Improve the web profile and perhaps provide full or part institute funding of PhD studentships from overseas.

- Weaknesses and threats:

The main threats appear to come from a lack of investment in sophisticated animal models to get their observations from humans. A major reorganisation and transfer of responsibilities. While this is a potential threat it is also an opportunity to deliver the next generation of leaders in the CRC.

- Recommendations:

The website should be developed to highlight the activity of the group and especially the new co-directors. This could also highlight opportunities for overseas appointments.

All efforts should be made to develop appropriate animal models to test observations made in humans. The availability of genetic models of appropriate cancer such as the one featured during the site visit presentation, including metastasis needs to be considered.

Every effort must be made to continue and strenghten the interactions with the clinical work, including patient material, data and collaborators.

Team 12 : Integrative Cancer Immunology Laboratory

Name of team leader: Mr Jérôme GALON

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	
N2: Permanent EPST or EPIC researchers and similar positions	1	1	
N3: Other permanent staff (without research duties)	1.5	1.5	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	4	
N6: Other contractual staff (without research duties)	1	1	
TOTAL N1 to N6	**6.5**	**8.5**	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	1	
Theses defended	7	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs

The Team is developing systems biology approaches with the aim to acquire a global understanding of the mechanisms put into play by the tumor to resist and to avoid the immune system (immunoediting and immune escape). In particular they have undertaken the precise analysis of the tumor microenvironment in Colorectal Cancer (CRC) through multiple integrative approaches (immunohistochemistry (IHC), flow-cytometric, transcriptomic,…).

They have developed critical interaction with clinicians and hospitals, especially the Service of Digestive Surgery, Laënnec-HEGP hospital, (including samples from 1986 till present), Avicenne hospitals (Besançon), Graz (Austria), Erlangen (Germany) and created a database (TME.db) agreed by CNIL including all clinical (samples, clinical data and follow-up information) and biological data.

They have deployed the technological infrastructure and the informatics (program development: ClueGo, PAthwayExplorer) and bioinformatics tools to master large-scale analyses (transcriptomics, IHC).

This systemic biology approach leads the team to convincingly demonstrate for the first time in humans the importance of the local immune response in the control of the tumor progression and the outcome of patient with primary CRC.

They have pioneered the Immunoscore (nature, functional orientation, density and location of immune cells infiltrating the CRC) with a particular emphasis on T cells and demonstrate in multivariate analysis in CRC, that this Immunoscore appears be the only parameter linked to the clinical evolution (DFS and OS); whereas the usual histo-prognostic criteria (T-Stage, N-Stage and tumor differentiation) then become not significant.

They are now involved in an international multicentric validation of the Immunoscore in the objective to use it as prognostic tools to adapt treatment and to help in the development of immunotherapies.

Their work represents an important breakthrough pointing the immune response as a dominant parameter in the outcome of patients with CRC. Furthermore, their methodological and technological development (database, bioinformatics tools, image analysis software, …) will permit standardization of the local immunological parameters in a Immunoscore of clinical value for treatment adaptation.

The team leader has a strong publication record and international recognition. The team has produced a total of 63 publications, 26 of which since 2007 (h-factor=25, >3,400 citations), with an IF >20: n = 3. Among the Journals, Science 2006, Nat Rev Cancer 2012, J Clin Oncol 2009, 2011, Gastroenterology 2010, Bioinformatics 2009, J Transl Med 2011, 2012a, 2012b, Nat Rev Clin Oncol. 2011, Curr Opin Immunol. 2010, 2011.

Average citations per paper published since January 2007 is 33.8 and publications were in the Top 1% most frequently cited papers in all disciplines. The international recognition can also be judged by his invitation to meetings: 30 National and 91 International invited lectures since 2007.

Assessment of the unit's academic reputation and appeal

The team currently has numerous active collaborations, both national and international with numerous papers in co-authorship.

7 National Collaborations (24 papers published)*:*

12 International Collaborations: Central collaboration with a reputed Austrian lab on Software and Application server and database development for cancer and functional genomic studies has yield 10 common publications. A multicentric Bioinformatics partnership for a genomic analysis pole has been created.

The team has received 15 national grants since 2007, including 7 multicentric projects coordinated by the team: INCA-Colon, PHRC: Immucol, Ville de Paris, CANCEROPOLE Ile-de-France, AVENIR INSERM, ARC, INCA Translationnel and 3 major international grants since 2007 : Qatar NPRP, MedImmune, EU-FP; for a total of 4 Millions € since 2007.

Distinctions, Prices: The team leader received several awards for his work on cancer and immunity: the silver medal of the Ville de Paris (Research Award, France in 2007), the AVENIR award (INSERM, 2006), the Schaeverbeke Award, (Foundation of France 2008), the Rose Lamarca Clinical Research Award (Medical Research Foundation 2008), the very prestigious William B. Coley Award (Cancer Research Institute, NY, USA, 2010), and the Cino del Duca Award from Academy of Science (France 2011), and Gallet et Breton Award from National Academy of Medicine (France 2011). One of the scientists was nominated at the Victoires de la Médecine (2006), and awarded by the Foundation de France (Jean & Madeleine Schaeverbeke, 2006).

National Invitations: Since 2009, 30 invitations to French congress/seminars.

International invitations: Since 2009, 61 invitations at international congresses, and 30 invited seminars. in 30 different countries besides France.

Congress Organization: Society for Immunotherapy of Cancer Workshop in Bethesda, USA, in October 2012; Conference on Immunoscore (Italy-1, Italy-2, Qatar).

Networks, Scientific Societies: The team is a member of the LAbEX 2011 ImmunoOncology; PACRI (National University-hospital network in Cancer), CARPEM (SIRIC. The team leader is associate-director and founder of European Academy of Tumor Immunology; board member of SITC, USA.

Training and visiting scientists: The team leader has directed 39 people: 10 Technicians, Engineers, 15 master students, 9 PhD fellows including 4 from abroad and 5 PostDoctoral fellows.

Editorial and evaluation committees: reviewers for 15 international Journals; grant evaluation for 7 international institutes: CR (UK), Fondazione Cariplo (Italy), HRC (New Zealand), and French: ARC, INCA, FRM...

Conclusion: All these factual elements illustrate the strong international recognition of his scientific contributions and its attractiveness.

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

- 30 patents and patents applications, - 4 contracts with industrial partners signed; - 8 other industrial partners on going.

- They have implemented a core facility on Immunoscore at the HEGP hospital.

- initiates the European Academy of Tumor Immunology (EATI), and a task force on “Immunoscoring as a New Possible Approach for the Classification of Cancer”. 21 international expert centers worldwide to validate the Immunoscore; - national multicentric (6 hospitals) prospective study (PHRC 2012).

- System biology approaches: HTS technologies and Bioinformatic infrastructure: functional databases: - development of software (PAthwayExplorer, ClueGO) used by > 1800 institutions worldwide.

- The team promotes their discovery and concepts through reviews highly cited in high impact journals (Nat Rev Cancer, J Transl Med, Nat Rev Clin Oncol, Curr Opin Immunol, Cancer Res).

- The team leader is involved in *patent meetings* with Inserm patent office (Conf-calls 1/week).

Assessment of the unit's organisation and life

Team organization: strongly operational structured group along to 3 main complementing research themes: i) Integrative cancer immunology (8 persons), ii) Bioinformatic development (8 persons), iii) Prospective validation of the immunoscore (3 persons).

Team management: The team leader participates in different internal team meetings (Laboratory meeting: 1/week, Individual follow up meeting: on a regular basis), Interlab meetings (- Inter-lab meetings with 3 different CRC groups, - “Journal-club” meeting: 1/week).

National and international Coordination: coordination of 12 collaborative projects for resources optimization, dissemination of protocols and results and decision-making including valorization and publication.

Conclusion: Although internationally demanded, the team leader is still deeply involved in supervising the research in his group. The lack of secretary dedicated to the team increases the weight of administrative duties on the team Leader.

Assessment of the unit's involvement in training through research

Student supervision: team affiliated to the Doctoral School in Physiology-Physiopathology of Paris VI-UPMC. 2 HDR () and respects the criteria for accepting doctoral students. 8 PhD students trained since 2007, 5 of them in co-direction with their privileged Austrian collaborator 7 have already graduated. 6 out these 7 have several publications (6-12), 5 >1 in first authors in high impact journals. All these 7 students are currently in postdoc in France except one in postdoc abroad.

Educational contribution: - One team member is member of the « commission pédagogique » and of TICE commission of the Faculté de Médecine Paris Descartes; - He is in charge of DU "Thérapeutiques Immunologiques" (Paris VI); - The team leader created a module of Systems Immunology in the master of UPMC (2011, 2012)

Teaching and implication in LMD formation program: 26-30h courses per year in M2,(Paris V, VI, VII, 11, 12, Paris-Sud, Descartes, UPMC, ENS Cachan, ENS Lyon, Toulouse),EPHE, DU, DUI (Paris VI, UPMC, Dijon).

Conclusion: Although the team has few permanent researchers and no "enseignant-chercheur", the team is actively involved in teaching both through forming high level PhD students but also through direct contribution in existing master courses and through creation of a module on Systems Immunology.

Assessment of the five-year plan and strategy

The program includes 4 projects: 1- Integrative Analysis of Tumor microenvironment in Human Cancer; 2- Identification of Colorectal Cancer Epitopes; 3- microRNA, prognostic signature and function; 4- Translational and clinical research. The major evolution of the program is linked to the objective to associate the tumor molecular alterations to the immune subpopulations and the tumor progression (project 1 and project 2). As an extension of their systemic biology approach they will also analyze miRNA profiles (project 3). Project 4 represents the continuation of the ongoing clinical validation of the Immunoscore.

Conclusion: The originality and consistency of the project rely on the system biology approach that previously allows the team to demonstrate the dominance of the immune contexture over the classical tumor parameters. It is based on a strong established scientific and methodological expertise in both immunology and bioinformatics. In addition to improving the established prognostic value of the Immunoscore, the system biology approach undertaken will bring important answers such as : i) the link between tumor alteration and immune parameters, ii) the link between the presence of immunogenic epitopes and the anti-tumor immunity and patient outcome, or conversely iii) the existence of immune evasion mechanisms linked to non immunogenic tumor molecular alterations.

Importantly the team has established strong collaboration with academic teams expert in bioinformatics (Innsbruck, Austria) or in tumor immunology (Labex Onco-Immuno), worldwide hospital for clinical validation, as well as industrial partners for industrial development.

Conclusion

● Strengths and opportunities:

- A team of young, competent and complementary experts (one clinician, one scientist): strong research program at the interface of basic and clinical research.

- Systems biology approach of a complex disease (cancer) and high technology development: Global analysis of immune reaction at the tumor site and precise dissection of tumoral regions; Large cohort of patients, human studies; High throughput technologies including most "omics" approaches.

- Bioinformatics infrastructure associated within the lab with bio-informaticians and biostatisticians: functional specific databases; Software development for data mining (PAthwayExplorer, ClueGO).

- Strong collaborative network with academic teams expert in bioinformatics (Innsbruck, Austria) or in tumor immunology (Labex Onco-Immuno), worldwide hospital for clinical validation, as well as industrial partners for industrial development.

- Multidisciplinary work and expertise: The multidisciplinary program has been bringing together surgeons, oncologists, immunologists and pathologists from different countries/hospitals.

- Strong publication records: Multicentric Work has resulted in the publications of teams in leading international journals attesting to their expertise and to the scientific relevance of this approach.

- Strong patents portfolio and industrial partnerships: 30 patents, >4 contracts with industry.

- High international recognition: high level highly cited publications, invited to international congresses (90 beside France), board member of international societies, consultant for pharma and biotechs.

- Major opportunities in commercial development: - Multiple patents; - Big pharma and biotech companies interested in licensing; - Collaboration with industrial partners; - Interest of venture capitals.

- Major opportunity in transfer Immunoscore in clinical use.

● Weaknesses and threats:

Weaknesses: The team and the project present few and marginal weakness:

- Among the 4 projects that are presented, the project 3 on miRNA seems relatively poorly connected to the other immunological approaches.

- The team leader mentions weakness in animal models that they will develop in the coming project. However their functional biology competence might need to be developed in the future in particular for project 1 and 2.

Threats: The team has many strong points, but with very limiting permanent researcher. The team suffers from:

- Few permanent positions for technician, engineer, researcher.

- Need permanent Bioinformatics researcher (bioinfo and biostat) to stabilize the bioinformatics infrastructure.

- Need to improve the administrative support of the team and the team Leader.

● Recommendations:

The bioinformatics resources both human and material should be strenghtened, this is a strategically valuable investment.

The team leader should be supported in such a way that he can maintain the leadership of the international initiative on validation of the “immunoscore” as a biomarker, clinical staging tool in coloreactal carcinoma. Interactions with other teams should be Actively strenghtened, particularly with new team 11 which is focusing on lung carcinoma and lung metastases from colorectal and renal cell carcinomas.The project 3 on miRNA should be more clearly linked to the immune response investigations.

A major limitation of theteam is its low number of permanent positions that need to be improved especially in bioinformatic. Recommendation to the team leader will be to also present young scientists to EPST recruitment process in the objective to strenghten his team with permanent scientists.

Team 13 : Immunopathology and therapeutic immunointervention

Name of team leader: Mr Srini KAVERI/ Mr Sebastien LACROIX-DESMAZES

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			
N2: Permanent EPST or EPIC researchers and similar positions	4	4	
N3: Other permanent staff (without research duties)	3	2	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2		
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**9**	**6**	

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

• Detailed assessments

Assessment of scientific quality and outputs

The team's work deals with several importants aspects of humoral and cellular immunology.

- Immunomodulation following intravenous administration of immunoglobulins (IVIg). IVIg are used in immunodeficiencies and in autoimmune diseases, and the group has a strong and long-standing expertise in the field. Various aspects of this type of treatment have been studied: influence on Tregs, on iNKT cells, on TH17 cells, activity of F(ab')2 fragments, stimulation of B cells. The group made here important observations.

- Polyreactivity of antibodies. In collaboration with a bulgarian group, the team analyzed how polyreactivity can be induced, for example by various protein destabilizing agents (pH, ROS, ferrous ions).

- Regulation of dendritic cells by Tregs. Generation of semi-mature DC, in the presence of Tregs, a collaborative work with a team located in Oxford. Participation in the developement of CCR4 antagonists, which could limit Treg migration.

- Immune evasion by fungal spores. As a collaboration they observed that surface GPI-anchored RodA hydrophobins does not induce DC maturation or activation. This very nice work indicates that these conidial cells are inert to innate and adaptive immunity.

- Mycobacterial cell wall antigens regulate DC and T cell activation. Together with colleagues in Bangalore, a study of cell wall antigens (proline-glutamic acid and proline-proline glutamic acid proteins) that trigger IL-12 production by DC, even when DC are under the influence of CTLA-4 or TGF-ß.

- Immune response to therapeutic factor VIII. Several aspects of the immunogenicity of FVIII have been investigated: mannosylated sugars important for endocytosis by antigen presenting cells, blocking of this endocytosis by von Willebrand factor, notion that in FVIII-deficient mice the activation of Heme-Oxygenase 1 prior to immunization reduces immune responses to FVIII.

- Catalytic anti-FVIII antibodies. The group showed that in acquired hemophilia patients treated with FVIII such antibodies can be present and contribute to treatment resistance. Discovery in the same patients of antibodies to FIX, which have a proteolytic activity and activate this factor. Presence of catalytic anti-FVIII and FIX antibodies in patients with a kidney allograft.

The group published since 2007 an important number (129) of articles of an excellent level such as PNAS, Blood, Mol Immunol, JBC, Nat rev Microbiol, J Immunol, Immunology.

Assessment of the unit's academic reputation and appeal

The group has an impressive number of productive national and international collaborations, and in particular with India.

The group has received 18 grants since 2007 (total of 2M €), about 50% of which are national. There are 5 contracts with industrial partners.

Since 2007 the laboratory has hosted 11 PhD students, 10 post-doctoral students, and 5 visiting scientists.

It is thus clear that the team is well recognized, and attracts excellent students.

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

The team has 5 contracts with industrial partners (Bayer Healthcare, CSL-Behring, LFB, Stago, Talecris/Grifols). It filed or is filing 6 patent applications. They have given numerous lectures in India, to high school children and college students. He has written popular scientific articles in indian weekly journals.

Assessment of the unit's organisation and life

There is no apparent problem, and on the contrary it was obvious during the visit they have built a closely-knit research team.

Assessment of the unit's involvement in training through research

The team is affiliated to the Doctoral School Physiology-Physiopathology of Paris 6-UPMC. So far 5 PhD have been completed, and 6 are ongoing. There is a participation to the european Erasmus programme, with one fellow in 2010-2012. As indicated above the laboratory is attractive to students and researchers. Team members participate in continued education programs by giving lectures in universities and pharma companies.

Assessment of the five-year plan and strategy

The proposed new management, with a co-directorschip by Mr Srini KAVERI and Mr Sebastien LACROIX-DESMAZES makes a lot of sense. The proposed 5-year plan builds up on the strong expertises of the group in the IVIg field, and on excellent collaborations to study immune evasion mechanisms of pathogens.

Conclusion

- Strengths and opportunities:

- Large group, well known, numerous publications, diverse research topics, excellent academic collaborations.

- Strong history of discoveries and developments in the field of polyclonal antibodies (effects on the imunne network, production at the time of infection, neutralizing activities on coagulation, and catalysis). Have used their collaborations with drug companies that sell IVIg. Excellent link to research centre in India.

- Weaknesses and threats:

It might be difficult to pursue all the lines of research concurrently.

As indicated in the document, more expertise in molecular biology would strengthen the team.

- Recommendations:

Support this dynamic group. Accompany the new team leadership (in their quest for scientific excellence through the implementation of new methodologies and if possible a small decrease in the number of research projects.

Encourage their links with India, including the recruitment of top-level students, a great opportunity for other CRC laboratories as well.

Team 14 : Physiopathology of ocular diseases

Name of team leader: Ms Francine BEHAR COHEN

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	9	
N2: Permanent EPST or EPIC researchers and similar positions	5	4	
N3: Other permanent staff (without research duties)	5	5	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	6	2	
N6: Other contractual staff (without research duties)	3		
TOTAL N1 to N6	**25**	**20**	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	11	
Theses defended	14	
Postdoctoral students having spent at least 12 months in the unit	5	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	8	8

• Detailed assessments

Assessment of scientific quality and outputs

The team has made an important discovery in the field of ophthalmology in a frequent disease of the retina called the central serous choroidopathy with a publication at the end of 2012 in J Clin Invest (IF 16.6). The immediate consequence of this discovery is the strong reinforcement of the central project of the team, i.e. mechanisms of retinal and macular edema (aim 3). Based on their discovery and on recent observations they propose an innovative hypothesis. The team developed also an innovative approach to inject in the eye, which is the suprachoroidal route, published in 2012 in 2 papers in Mol Ther (IF 6.5). More recently, the team invented the ciliary muscle electroporation to transiently provide protein drugs in inflammatory eyes and in the following the team created the biotech company Eyevensys to test this route in clinics. It is also interesting to note a new expertise of the team in the field of the vitreoretinopathy based on recent results (N Engl J Med 2012 IF 53.4).

Since 2007, the team has produced 157 peer-reviewed papers, including 71 directly originating from the team and 85 in collaborations, plus 42 publications from recent team members. 10 papers have an IF>10, 19 with IF between 5 and 10, and 81 with an IF between 3 and 5 (note that Investigative Ophthalmology and Visual Sciences, which is the top journal in ophthalmological research has an IF of 3.9. When looking at publications as first or last author, 15 publications have an IF > 5 and 4 publications of recent team members have an IF > 5.

Assessment of the unit's academic reputation and appeal

The team leader is an internationally renowned researcher and a vitroretinal surgeon, with a very strong background in retinal pathophysiology and pharmacology. She was a member of INSERM CSS 01 until 2012. She organized a symposium at the international ocular pharmacology meeting in China in 2010 and 5 other symposiums in France She is reviewer of Nature, JCI, FASEB J, IOVS, and other journals.

The Team also has 24 national collaborations, 17 international collaborations ; 40 grants since 2007, including one ERC for a researcher who now left the CRC. Among the 40, there are 12 ANR (including 4 ANR emergence) and 3 from Europe. Altogether it accounts for 4,677 M€, including the ANR mineraloRet. The team also attracted several renowned foreigner researchers.

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

This is a very strong aspect of the Team: there are 9 patents, 4 have been licensed. The team leader is a SAB member for 7 companies (Essilor, Novartis, Pfizer…). She has obtained 2 OSEO ANVAR prices (2006 and 2007). The team received a POC specific support from Inserm for project with high valorization impact. It has a COFECUB research exchange program with Brazil (Paris 13). It has obtained a research grant for collaborative program with ANSES (2011) and a funding to organize an international symposium from the French Ministry of Environment and Health. The team obtained two “contrat d’interface” with Inserm hospital for the funding of MD-PhD involved in translational research (2005-2008 and 2008-2011).

- A biotech company has emerged from the team : Eyevensys SAS, that is incubated in the lab and which has been funded in 2012

- There are 4 clinical trials directly translated from the team research:

    - A first trial in 12 patients with CRSC
    - A second control study in a larger cohort with CRSC
    - An escalating dose of peptides inhibiting JNK pathway subconjonctivally in 40 patients
    - A multicentric phase II with Solvay Abbot started in 2012

- Publication of a book on age-related maculopathy distributed for free to 20 000 patients

- Organization every year in collaboration with the Lions Club of two open days for free diagnosis of ocular diseases (more than 600 patients are screened every year)

- Participation to open information days on ocular diseases at the Mairie du 4ème and at Villecresnes.

- Creation of a patient association CRO “tous unis pour la vision”with 4 meetings a year.

- One participant had a “contrat d’interface” with the Ecole Nationale Vétérinaire d’Alfort for bilateral research collaboration (2008/2011). The team has an ECOS research exchange program with Uruguay (Paris 13). The team has also a research program with the ADEME (Agence Environnement et Maîtrise de l’Energie) and CSTB.

- One participant has a “contrat d’interface” with Inserm (2011-2014).

- One researcher obtained a Marie-Curie reintegration grant (2011-2012).

- The team leader has been President of the study group on LED (light emitting diodes) of the 3D tech group of the national agency for the security and environment, member of the EU committee SCENIHR (emerging technologies). She edited a report to guide a decret on the limitation of free diffusion of LED light belonging to class 1 or more.

Assessment of the unit's organisation and life

This is a large team in which there seems to be easy communication. The way the project is developed suggests a logical organization between the different aims of the project. Group members and technicians are shared by several aims (projects).

Assessment of the unit's involvement in training through research

Since 2006, 10 PhD students defended their thesis. There have been also 9 master students and 2 engineers. Currently, there are 10 PhD students in the lab and 4 master 2 students. The team is affiliated to Doctoral School: GC2ID (UPD) and Ecole Doctorale médicament (UPD).The team is involved in LMD formation program.

Assessment of the five-year plan and strategy

The project is very well thought. It is based on several well documented hypothesis and preliminary results, as the involvement of mineralocorticoid receptors in central serous choroidopathy, or in various forms of macular edema.

The project has been well centered around this central theme, and it allows to branch to the most frequent pathologies in retina, which are diabetic retinopathy and age-related maculopathy, although animal models for diabetic retinopathy are not excellent.

There is a good balance between laboratory work and clinical trials, with a very efficient valorization and transfer to clinics.

The feasibility of the project is excellent for the most important aims. A few other aims are minor (less than ¼ of the total) and are less feasible, but they could represent interesting developements in the future.

In perspective, not mentioned in the written document but orally presented at the visit, the creation of a Franco-Swiss network for vision research bridging together the team and the CHUV (Hôpital cantonal Universitaire de Lausanne), will allow to share clinical resources at the eye hospital Jules Gonin in Lausanne for clinical trials. In addition, techniques, expertise, tools, space and students will be shared, therefore increasing the visibility for the French and Swiss teams and allowing for additional funding resources.

Conclusion

- Strengths and opportunities:

This team represents a strong example of successful intra-center cooperation (with team 1) leading to a major discovery in the metabolism of an ophthalmic disease

This discovery is opening a vast field of investigations and importantly, will probably lead to a completely novel treatment for this ophthalmic disease, including the benigns forms (which may resolve spontaneously) but also for the recurrent and severe forms.

There is a strong impulse of the team leader who is both an expert clinician/surgeon in vitreoretinal disease and a researcher (formerly INSERM CR1). She progressively oriented the themes of her laboratory towards very relevant clinical issues.

Because of the team leader activities, of her many relationships with foreign collaborators and of her clinical duties in Paris Hotel Dieu, very strong transfer between clinics and laboratory work were developed. Thus, vitreous and retinal cells of patients could be analyzed.

The clinical valorization is excellent. Two biotech companies have been created, whose one is now on its way in USA, and the other (Eyevensys), recently created, is incubated in the laboratory. This efficient merge of biotechs by this lab is based on the creativity of the team in the domain of intraocular delivery, and on the world leadership of the team leader in this field. Remarkably, the team recently invented one new route, i.e. the electroporation of the ciliary muscle developed in Eyevensys biotech.

There is an excellent overall coherence of the project. The link between the aims working on CFH, macular edema, MR and intraocular routes is clear. There are good theme relationships and members of the team participate to several themes. There is a very good feasibility of the project.

The scientific production is excellent.

- Weaknesses and threats:

Young researchers, except for one case who has been recruited as a CR2 INSERM, do not have secured positions, making it possible that parts of the developing project could not be achieved if they leave. Also, the interesting hypothesis on diabetic retinopathy and AMD require full time researchers for an efficient development. The 3 research directors need to recruit CR researchers.

The Hôtel Dieu hospital is going to be closed, so the very good clinical transfer may weaken, therefore needing to be efficiently organized with other hospitals.

The Team leader mentioned a relative lack of national visibility (while she is widely recognized at an international level!)

- Recommendations:

There is an urgent need to focus efforts on recruitment of young full time researchers.

Team 15 :

Cell death and drug resistance in lymphoproliferative disorders

Name of team leader:

Mr Santos SUSIN

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	4	
N2: Permanent EPST or EPIC researchers and similar positions	2	2	
N3: Other permanent staff (without research duties)	4	4	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2	
N6: Other contractual staff (without research duties)	2	2	
TOTAL N1 to N6	**14**	**14**	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	6	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	5	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	5	5

• Detailed assessments

Assessment of scientific quality and outputs

Over the past five years, this team has produced very interesting results on caspase-independent cell death. In particular the team has shown that Drp1 and mitochondrial fission play a role in this process. This team has also investigated the mechanism of action of AIF and reported an intriguing connexion with H2AX. In addition, the team has shown that activation of CD47 triggers death of apoptosis-resistant CLL (chronic lymphocytic leukemia). Interestingly, a peptide made of the last 10 amino acids of Thrombospondin 1, a ligand of CD47, was shown to trigger caspase-independent cell death of CLL. One of the main goals of the team is to test the peptide in vivo, using a mouse model of CLL, and ultimately to produce a drug using this peptide.

Since 2007, the group has published 40 papers (10 with an IF> 10, such as Blood, EMBO Journal, CDD, MCB) in which the PIs of the lab are 1st or last authors. In addition, as a result of many national and international collaborations, members of the team are co-authors on 67 papers.

Assessment of the unit's academic reputation and appeal

There is a discrepancy between the quality of the data produced by the team and the international visibility of the team leader. Most of it may be due to insufficient participation of Dr Susin at international meetings. However, it has to be mentioned that the other PIs of the team have been invited to participate in a substantial number of national and international symposia. On the good side, however, the team has attracted 5 foreign PhD students, a testimony to its attractiveness.

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

The team is well funded (2.9 M euros since 2007). Importantly, the team has been able to obtain 5 contracts with industrial partners. Three patents have been filed.

Assessment of the unit's organisation and life

The team is relatively small and is composed of 5 PhD students, 2 post-docs, 4 clinicians, one senior scientist (CR1) and 6 engineers/technicians. The collaboration between pure scientists and MDs appears to work well. MDs are well integrated in the team. Not only do they participate in the two main projects (AIF and CD47), but they have been able to develop their own projects. Currently the support of these projects is limited and should be increased in the future, which would require additional recruitment (PhD, post-docs).

Assessment of the unit's involvement in training through research

The team is currently hosting 5 PhD students. Since 2007, 11 PhD students, 13 Master students and 2 Erasmus students have been trained in the lab which is remarkable.

Assessment of the five-year plan and strategy

The projects that will be pursued in the following years are of key interest. They aim at: i) understanding the mechanism of caspase-independent cell death as well as the mechanism of action of AIF through the analysis of a recently developed mouse model, as explained above; ii) testing a CD47-activating peptide in mouse models of CLL and in cells from patients, improving the stability, biodisponibility of the peptide and if everything goes well, testing the peptide in patients. The presence of clinicians in the team is essential for the progression and success of this project.

Conclusion

- Strengths and opportunities:

The team is working on interesting projects, and the results that are produced can be trusted.

The team leader is able to attract good PhD students and post-docs.

Excellent integration of clinicians in the team.

The team has excellent expertise on the biology of mitochondria and on cell death and the projects they work on are feasible.

The mouse model with a knockin of AIF lacking the putative killing C-terminal domain should help to characterize the active function of AIF in cell death, if any.

The collaboration with clinicians for the work on CLL is definitely a plus.

Good network of collaborations (national and international).

The team has been successful at raising funds.

- Weaknesses and threats:

The group needs to acquire a better international visibility. The team has very few collaborations with other teams of the CRC and there are novel opportunities for synergies in the new CRC project.

- Recommendations:

Attend key international meetings, meet with the leaders in the field and present their data as oral presentations. Organize international meetings on caspase-independent cell death.

Collaborate with other teams of the CRC, so as not to appear isolated and marginalized in this large institution.

Increase human resources in projects aiming at deciphering the mechanisms underlying drug resistance in CLL.

Team 16 : Information Sciences to support Personalized Medicine

Name of team leader: Ms Anita BURGUN

Workforce : New team without past as such. The workforce is thus given only for the project

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		8	
N2: Permanent EPST or EPIC researchers and similar positions		1	
N3: Other permanent staff (without research duties)		2	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		2	
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6		**13**	

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

• Detailed assessments

As a preamble, two short points:

- The Team is a new one (established Spring 2012, as an “équipe en émergence”), making it difficult to assess any output at this stage. The assessment presented below is essentially based on the written request (research agenda and composition of the team).

- Having such a public health oriented team is a major step for the development of the CRC, providing an expertise in population medicine, biostatistics and informatics techniques.

Assessment of scientific quality and outputs

This group has been involved in the creative generation of bioinformatic tools for the next generation analytical and synthetic work with large amounts of data from high throughput technologies. They have been very active in identifying biomarkers for both diseases and therapies. Members of the team coordinate one ANR project and participated in 3 EU projects related to medical data integration. They published approximately 250 original articles since January 2007, one third of which corresponds to research on novel methods for scientific and biomedical data management.

Assessment of the unit's academic reputation and appeal

The team is at the very beginning of its development. No criteria available to assess this point. However, most of the participants have developed a good academic reputation before the beginning of this team.

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

The team is at the very beginning of its development. No criteria available to assess this point. Potentially however, there is a very strong argument for having this sort of public health, biostatistics, bio-informatics oriented team included in the CRC.

Assessment of the unit's organisation and life

The team is at the very beginning of its development. No criteria available to assess this point.

Assessment of the unit's involvement in training through research

The team is at the very beginning of its development. No criteria available to assess this point.

Assessment of the five-year plan and strategy

The proposed program is a wise one, presenting most of the current issues in personalized medicine. The strong emphasis on Information Technologies is most welcome, for the management of huge databases is and will be key for this sort of program, aiming the transformation of data into information relevant for clinical and epidemiologic analysis.

A further strong point is that the team already has an access to an existing database: the data warehouse of Hôpital-Européen-Georges-Pompidou. The team seems to have already an experience in accessing and working with this database.

There is one main concern. As of now, there is nobody in this team who is familiar with genetic epidemiology and/or genetic statistics. This part of observational epidemiology is an important one for the development of personalized medicine, e.g., to analyze and to interpret the heterogeneity across patients and populations.

Another important contribution of epidemiology is the characterization of life course markers and for the identification of critical periods for the development of diseases.

Developing these two competencies and skills (genetic epidemiology and/or genetic statistics, life course epidemiology) should be part of the strategic development of the team.

Another aspect is related to screening. Two out of the five objectives of personalized medicine are:

- Detect the onset of disease at the earliest moments, based on identified biomarkers that arise from changes at the molecular level.

- Pre-empt the progression of disease, as a result of early detection.

Both objectives are in fact relevant to any program aiming the development and evaluation of a screening strategy (or early diagnostic). If the development of personalized medicine includes the identification of new screening strategies (e.g., identification of genetics or molecular markers for screening of chronic diseases), a strong collaboration should be established with existing teams working on screening strategies.

In general, personalized medicine is an ambitious project, in terms of clarification of the etiology and the etiopathology of different diseases, development of life-course markers, development of practical tips for the prevention and the treatment of diseases, etc. It is unlikely that all these challenges will be successful within the coming 5 years. In this perspective, more specific, practical, achievable objectives should thus be proposed for the end of five coming years.

The field of personalized medicine is already very competitive. The committee wonders how far a better delineation of research fields should be made, with some focus on specific issues. For example, the impression is that cancer is already widely studied by several advanced teams. There are however other chronic diseases of public health relevance, such as cardiometabolic diseases, neuropsychiatric diseases (especially depression and degenerative dementia) and musculoskeletal conditions. It could be easier for this new team to gain visibility by concentrating on these latter conditions. In this perspective, within the CRC, strong relationships with the teams dealing with nutrition, and/or lipids and/or metabolic diseases could be developed.

Conclusion

- Strengths and opportunities

Young and active team, building up on a strong experience in various fields, all related to personalized medicine.

Several strong aspects of the programs, including the fact that several participants have a background in public health, clinical epidemiology, and clinical trials.

- Weaknesses and threats:

The field is very competitive, with several teams working since several years on personalized medicine: it could be difficult to gain a strong profile, with practical results and with international visibility. However, the committee of experts understands that the team already has formal relationships with strong partners.

- Recommendations:

The team would be strengthened if more people educated and experienced in epidemiology, more specifically in genetic epidemiology of complex diseases.

It could be useful to explore the possibility of developing personalized medicine in other public health relevant fields such as cardiometabolic diseases or mental health.

5 • Conduct of the visit

Visit dates:

Start: January 21, 2013, at 8 30 am

End: January 23, 2013, at 1 30 pm

Visit site: Centre des cordeliers, Paris

Conduct or programme of visit:

See program on next page

	SCIENTIFIC PROGRAM		
Monday		**Participants**	**Place**
8h15-8h30	Committee welcome		Room XX
8h30-9h00	Closed session	Committee members and AERES representative	Room XX
9h00-9h15	Presentation of the committee members and the evaluation process by the committee President	Committee members, AERES representative, Directors and Deputy, Team leaders	Room XX
9h15-11h15	CRC: Past by the Director, Future by the project leader and the department directors, Core facilities, Questions	Committee members, AERES representative, Directors and Deputy, Team leaders, staff	Room XX
11h15-12h30	Meeting with PhD students and post-docs	Split Committee	**Room XX**
11h15-12h30	Meeting with engineers, technicians and administrative assistants	Split Committee	**Room XX**
11h15-12h30	Meeting with researchers (permanent positions) except Team leaders, Directors and Deputy Director	Split Committee	**Room XX**
12h30-13h45	**Lunch on site** **Partition of the 2 department committees**	Committee members and AERES representative Directors and Deputy, Team leaders	**Room XX**
Dept 1			
13h45-15h00	Team 1: F. Jaisser (Presentation 30', questions '30, Committee discussion 15')	Committee members and AERES representative, Directors or Deputy	**Room XX**
15h00-16h15	Team 2: R. Roussel (Presentation 30', questions 30', Committee discussion 15')	Committee members and AERES representative, Directors or Deputy	**Room XX**
16h15-16h30	**Break**		**Room XX**
16h30-17h45	Team 3: A. Edwards (Presentation 30', questions 30', Committee discussion 15')	Committee members and AERES representative, Directors or Deputy	**Room XX**
17h45-19h00	Team 4: A. Leturque (Presentation 30', questions 30', Committee discussion 15')	Committee members and AERES representative, Directors or Deputy	**Room XX**
	End of the scientific day for Dpt 1 committee		
Dept 2			
13h45-15h00	Team 13: I. Cremer/JL. Teillaud (Presentation 30', questions 30', Committee discussion 15')	Committee members and AERES representative Directors or Deputy	**Room XX**
15h00-16h15	Team 15: J. Galon (Presentation: 30', questions 30', Committee discussion 15')	Committee members and AERES representative, Directors or Deputy	**Room XX**
16h15-16h30	**Break**		**Room XX**
16h30-17h45	Team 16: S. Kaveri/S. Lacroix-Desmaze (Presentation:30', questions 30', Committee discussion	Committee members and AERES representative, Directors or Deputy	**Room XX**
17h45-19h00	Team 10: V. Frémeaux-Bacchi (Presentation:30', questions '30, Committee discussion 15')	Committee members and AERES representative, Directors or Deputy	**Room XX**
	End of the scientific day for Dpt 2 committee		
Tuesday		**Participants**	**Place**
Dept 1			
8h30-9h45	Team 6: D. Gauguier (Presentation:30', questions 30', Committee discussion 15')	Committee members and AERES representative, Directors or Deputy	**Room XX**
9h45-11h00	Team 8: F. Foufelle (Presentation:30', questions 30', Committee discussion 15')	Committee members and AERES representative, Directors or Deputy	**Room XX**
11h00-11h15	**Break**		
11h15-12h30	Team 5: A. Berdal (Presentation:30', questions 30', Committee discussion 15')	Committee members and AERES representative, Directors or Deputy	**Room XX**
Dept 2			
8h30-9h45	Team 11: G. Kroemer (Presentation:30', questions 30', Committee discussion 15')	Committee members and AERES representative, Directors or Deputy	**Room XX**
9h45-11h00	Team 22: A. Burgun-Parenthoine (Presentation 30', questions 30', Committee discussion 15')	Committee members and AERES representative, Directors or Deputy	**Room XX**
11h00-11h15	**Break**		
11h15-12h30	Team 19: S. Susin (Presentation 30', questions 30', Committee discussion 15')	Committee members and AERES representative, Directors or Deputy	**Room XX**
12h30-13h45	**Lunch on site**	Committee members and AERES representative Directors or Deputy	**Room: XX**
Dept 1			
13h45-15h00	Team 17: F. Behar-Cohen (Presentation:30', questions 30', Committee discussion 15')	Committee members and AERES representative, Directors or Deputy	**Room XX**
15h00-16h15	Team 12: M. Arthur (Presentation:30', questions 30', Committee discussion 15')	Committee members and AERES representative, Directors or Deputy	**Room XX**
Dept 2			
13h45-16h15	Committee for Dept 2 closed session	Committee 2 members and AERES representative,	
16h15-17h15	**Whole committe closed session (discussion on the CRC)** If requested, they can meet the Directors	Committee members and AERES representative,	**Room XX**
17h15-17h30	**Break**		**Room XX**
17h30-18h30	Meeting of the whole committee with trustees (Universities Paris 6, Paris 5 and Inserm)	Committee members and AERES representative,	**Room XX**
End of the Day	**End of the visit for Dept 2 experts**		
Wednesday		**Participants**	**Place**
8h45-12h00	Committee for Dept 1 closed session (break when necessary)	Committee 1 members and AERES representative,	**Room XX**
12h00-13h15	**Lunch**		**Room XX**
13h15-15h00	Meeting of the Committee President and Vice-President. If requested, they can meet the Directors	Committee members and AERES representatives,	**Room XX**
End of the Visit			

Date and conduct of the visit:

The AERES visit to the CRC, Paris, took place throughout January 21 to 23, 2013. The visit began with a short closed session with presentations by the AERES coordinator and the Committee President who gave instructions to the Committee and explained the AERES evaluation process.

The first session in the presence of all CRC members, started with an overview of the past activities given by Present Director (Mr Hervé Fridman) and of the future plans for the Center by the project leader, P Ferré. In addition the core facilities were presented by their scientific supervisor, and the two department coordinators presented their departments. Altogether, a complete overview of the Institute in terms of its scientific research, organization, source of financing, and main scientific themes was presented.

For the second session, the site visit committee splitted in three groups to meet i) The engineeers, technicians and administrative assistants; ii) the PhD students and post docs; iii) the researchers with a permanent position except Team Leaders, Directors and Deputy Directors.

The committee then split into two sub-committees, one for each department, in order to evaluate the individual research teams. This was necessary, due to the size of the Centre, in order to allow each team leader, in the presence of all team members, to have the opportunity to present his/her past activities and program during 30 min, followed by 30 min questions, and then 15 min were used for committee discussion in closed session. The first subcommittee was chaired by Ms Yannick LE MARCHAND-BRUSTEL, and reviewed the teams of Department I: Integrative Physiology and Physiopathology. The second subcommittee was chaired by Mr Pedro ROMERO and reviewed the teams of Department II : Cancer, Immunology and Immunopathology.

While sub-committee I continued to examine the teams from Department 1 on day 2, sub-committee II held its closed session in the afternoon. Then the entire committee met in a closed session for a discussion of the CRC as a whole, followed by a meeting with the representatives of the Trustees. This was the end of the visit for the members of sub-committee II.

On the last day, there was a closed session for the sub-committee I members, together with the chair of sub-committee II, for the final conclusions. There was also time for a short discussion with the project leader, the project deputy director, the current CRC director, and the two designated department scientific coordinators.

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

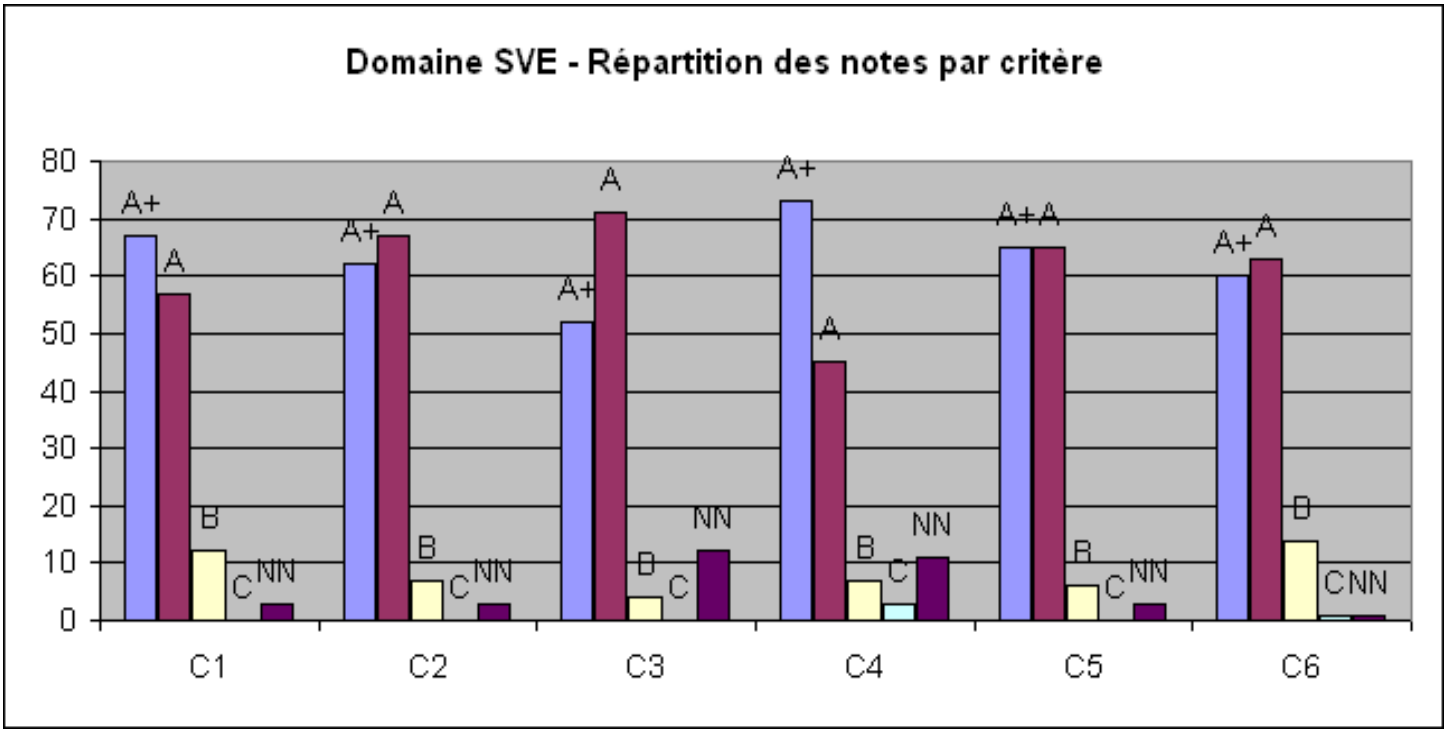
Grades

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

Percentages

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

Histogram



7 • Supervising bodies' general comments

Paris le 10 04 2013

Le Président
Didier Houssin
Agence d'évaluation de la recherche
et de l'enseignement supérieur
20 rue Vivienne - 75002 PARIS

M. le Président,

Nous avons pris connaissance avec le plus grand intérêt de votre rapport concernant le projet Centre de Recherche des Cordeliers, porté par M. Ferré. Nous tenons à remercier l'AERES et le comité pour l'efficacité et la qualité du travail d'analyse qui a été conduit.

Ce rapport a été transmis au directeur du laboratoire qui nous a fait part en retour de ses commentaires que vous trouverez ci-joint. Nous espérons que ces informations vous permettront de bien finaliser l'évaluation du laboratoire.

Restant à votre disposition pour de plus amples informations, je vous prie de croire, M. le Président, à l'expression de mes salutations respectueuses.

Le Vice -Président Recherche et Innovation

Paul Indelicato

Vice-présidence Recherche et Innovation
Tél. 01 44 27 20 09
www.upmc.fr

Pascal Ferré
Centre de Recherches des Cordeliers
15 rue de l'école de médecine,
75006 Paris

Le 8 avril 2013

Madame, Monsieur,

Au nom de l'ensemble du personnel du Centre de Recherche des Cordeliers, je tiens tout d'abord à remercier très sincèrement les experts du Comité de visite AERES et plus particulièrement ses Président et Vice-Président pour les échanges lors de la visite, pour la qualité du travail effectué et pour les recommandations constructives concernant le Centre et les équipes, que nous ne manquerons pas de prendre en compte.

Vous trouverez ci-dessous des réponses à un certain nombre de points soulevés dans le rapport.

Veuillez agréer, Madame, Monsieur, mes respectueuses salutations

Professeur Pascal Ferré

Comments concerning the Cordeliers Research Centre (P. Ferré)

I would like to comment here some of the key recommendations of the report.

- Concerning the Centre policy, it is mentioned that we must promote the arrival of new teams while preserving a good quilibrium between the two departments (departure of the team of Karine Clément in department 1, arrival of the team of Guido Kroemer in department 2). This will be a priority in the coming months in order to launch a first call in september/october. It will concern a young researcher who can apply for an “Atipe-Avenir” grant and works on a topic complementary to those developed in department one. We have already sufficient place to welcome such a movement. This will be completed later on by one or two other calls possibly for a larger group when more free space will become available after the departure of teams not included in the next contract.
- Another important aspect is to develop the international visbility of the CRC. I have asked our new communication and scientific animation manager to focus particularly on this aspect in order to develop a more robust policy concerning communication outside the Centre and particularly at the international level, through the more frequent invitation of foreign speakers, the development of a new website and the establishment of direct contacts with similar centers in the world. This should ease the recruitment of international post-docs (the new human resource manager will develop a desk allowing to help foreign staff for the administrative (e.g. visa) and practical (e.g. lodging, guarantees) aspects).
- It is stated that we must recruit young researchers and technicians in the teams since a number of researchers/technicians will retired during the next contract. Obviously, every team and the CRC management have made, are making and will make efforts to do so but it does not depend solely on them and the present and near-future situations are not particularly conducing concerning employment in research.

Comments by the Teams of the Cordeliers Research Centre (Team leaders)

In the AERES report, it has been chosen to change the team numbering when compared to the current team numbering in the CRC.
We present below the equivalences for an easier reading:
Team 1 (CRC) => Team 1 (AERES report)
Team 2 (CRC) => Team 2 (AERES report)
Team 3 (CRC) => Team 3 (AERES report)
Team 4 (CRC) => Team 4 (AERES report)
Team 5 (CRC) => Team 5 (AERES report)
Team 6 (CRC) => Team 6 (AERES report)
Team 8 (CRC) => Team 7 (AERES report)
Team 10 (CRC)=> Team 8 (AERES report)
Team 11 (CRC)=> Team 9 (AERES report)
Team 12 (CRC)=> Team 10 (AERES report)
Team 13 (CRC)=> Team 11 (AERES report)
Team 15 (CRC)=> Team 12 (AERES report)
Team 16 (CRC)=> Team 13 (AERES report)
Team 17 (CRC)=> Team 14 (AERES report)
Team 19 (CRC)=> Team 15 (AERES report)
Team 22 (CRC)=> Team 16 (AERES report)

Teams 1, 3, 5, 6, 7, 8, 9, 10, 12, and 14 (AERES report numbering) made no comments on the report.

Team N° 2 : Pathophysiology and therapeutics of vascular and renal diseases related to diabetes and nutrition (Ronan ROUSSEL)

We appreciate the highly positive comments made by the committee concerning our activity and project. We only would like to address a comment concerning the topic of vasopressin in part 2 of the project, challenging hypothesis of a role for this hormone in diabetes and its complications. We draw attention to recent publications from the team and from competitors An ERC-starting grant has been obtained on the topic of vasopressin and diabetes.

-Vasopressin: a novel target for the prevention and retardation of kidney disease? Bankir L, Bouby N, Ritz E. ***Nat Rev Nephrol***. 2013 Feb 12;9(4):223-39. Epub 2013 Feb 26.

-Plasma copeptin and renal outcome in patients with type 2 diabetes.. Velho1 G,Bouby N, Hadjadj, Matallah N, Fumeron F, Potier L, Bellili-Munoz N, Taveau C, Alhenc-Gelas F, Bankir L, Marre M, Roussel R ***Diabetes Care*** 2013 in revision
-Copeptin, a marker of vasopressin, in abdominal obesity, diabetes and microalbuminuria: the prospective Malmö Diet and Cancer Study cardiovascular cohort. Enhörning S, Bankir L, Bouby N, Struck J, Hedblad B, Persson M, Morgenthaler NG, Nilsson PM, Melander O.***Int J Obes (***Lond). 2012 May 22. doi: 10.1038/ijo.2012.88.
-Sex differences in the association between plasma copeptin and incident type 2 diabetes: the Prevention of Renal and Vascular Endstage Disease (PREVEND) study.Abbasi A, Corpeleijn E, Meijer E, Postmus D, Gansevoort RT, Gans RO, Struck J, Hillege HL, Stolk RP, Navis G, Bakker SJ.***Diabetologia.*** 2012 Jul;55(7):1963-70.
-Low water intake and risk for new-onset hyperglycemia**.** Roussel R, Fezeu L, Bouby N, Balkau B, Lantieri O, Alhenc-Gelas F, Marre M, Bankir L; D.E.S.I.R. Study Group. ***Diabetes Care***. 2011 Dec;34(12):2551-4.
-Copeptin levels associate with cardiovascular events in patients with ESRD and type 2 diabetes mellitus. Fenske W, Wanner C, Allolio B, Drechsler C, Blouin K, Lilienthal J, Krane V; German Diabetes, Dialysis Study Investigators.***J Am Soc Nephrol***. 2011 Apr;22(4):782-90..
-Copeptin, a surrogate marker of vasopressin, is associated with microalbuminuria in a large population cohort. Meijer E, Bakker SJ, Halbesma N, de Jong PE, Struck J, Gansevoort RT. ***Kidney Int***. 2010 Jan;77(1):29-36.
-Copeptin, IGFBP-1, and cardiovascular prognosis in patients with type 2 diabetes and acute myocardial infarction: a report from the DIGAMI 2 trial. Mellbin LG, Rydén L, Brismar K, Morgenthaler NG, Ohrvik J, Catrina SB. ***Diabetes Care***. 2010 Jul;33(7):1604-6.
-Plasma copeptin and the risk of diabetes mellitus. Enhörning S, Wang TJ, Nilsson PM, Almgren P, Hedblad B, Berglund G, Struck J, Morgenthaler NG, Bergmann A, Lindholm E, Groop L, Lyssenko V, Orho-Melander M, Newton-Cheh C, Melander O.***Circulation*** *(AHA)**.*** 2010 May 18;121(19):2102-8.
-Alteration of glucose homeostasis in V1a vasopressin receptor-deficient mice. Aoyagi T, Birumachi J, Hiroyama M, Fujiwara Y, Sanbe A, Yamauchi J, Tanoue A. **Endocrinology.** 2007 May;148:2075-84.
-Vasopressin contributes to hyperfiltration, albuminuria, and renal hypertrophy in diabetes mellitus: study in vasopressin-deficient Brattleboro rats. Bardoux P, Martin H, Ahloulay M, Schmitt F, Bouby N, Trinh-Trang-Tan MM, Bankir L. ***Proc Natl Acad Sci U S A***. 1999 Aug 31;96(18):10397-402

Team N° 4 : Intestine : nutrition, barrier and diseases (Armelle Leturque)

We would like to thank the AERES committee for the positive evaluation and helpful recommendations for our team project. In reponse to the comment “The project needs to be more focussed” we would like to underline that we will give highest priority to mechanistic aspects relevant to enteroendocrine lineage and function in response to nutrient sensing and to desmosomes as signaling platforms for intestinal barrier function. Complementary studies on microbiota (axis 1), ER stress (axis 2) and autophagy (axis 3) will be conducted in collaboration with experts in these fields.

We would like to give some missing or incomplete information. The number of PhD students in 2014 is expected to be 4 to 6, based on our past training activity, on the success of our master students to obtain doctoral contracts and on the number of "HDR" in the team. In the past five years, over 12 PhD students, we have trained 4 foreign PhD from Brazil, Lebanon, Mali, Palestine and over 4 post-doctoral fellows, 1 came from Germany.

We would like also to mention that the team is coordinator of an international ANR grant ALIA Nutra2sense.

Team N° 11: Cancers, Immune Control and Escape (Isabelle Cremer / Jean-Luc Teillaud)

First, we would like to thank the AERES committee and the experts who reviewed our work and proposal for their kind comments on “our internationally recognised force who helped mould our current understanding of cancer immunology” (former Team 13, C. Sautès-Fridman) and on the delivery of “some important work particularly showing the possibility that antibody serotherapy with anti-CD20 could promote acquired immunity” (former Team 14, JL Teillaud).

In order to further help our colleagues in the overall evaluation of our activities and proposal, we would like to highlight a few issues that are exposed and discussed in greater details in our reports.

Concerning the assessment of our interaction with the social, economic and cultural environment, we would like to point out that both teams have developed strong interactions with the industry over the years. Former Team 13 has a large collaborative work with the US firm MedImmune focusing on tumour micro-environment that is still on-going, while former Team 14 had a major input in the characterisation and optimization of low-fucose therapeutic antibodies by the French public firm LFB (anti-Rhesus D roledumab and the anti-CD20 ublituximab) that have undergone successfully Phase I and II trials and will be engaged in Phase III clinical assays.

We would like also to pinpoint that both Teams had/have a major involvement in teaching activities as five out of seven senior scientists are Professors or Assistant-Professors and the two remaining who belong to INSERM are largely involved in teaching activities (between 20-25 hours/year) as detailed in the reports. Prof. C. Fridman is the Head of the Immunology Master Specialty of Paris (3 different Universities) and as noted, Prof. I. Cremer is the Head of one of the Doctoral Schools of the Pierre et Marie Curie (UPMC)-Paris 6 University.

Also, members of the Teams are actively involved in international and national activities at the forefront of cancer immunology and immunotherapy. Prof. W.H. and Prof. C. Fridman are co-organizing yearly European courses (EFIS-EJI Summer School in Clinical Immunology whose third meeting will be held in Paris on next July 2013) and their retirement is not imminent. Dr Teillaud is a current member of the Executive Board of the French Society for Immunology (SFI) where he is acting as treasurer and, as such, is strongly involved in the organization committee of the annual SFI meetings. He has also recently organized the first French-Israeli meeting on B cells and antibody.

All these teaching and meeting activities gave us the opportunity to recruit Ph.D. and M2 students from abroad. We would like to mention that among the Ph.D. students currently in former Team 13, three of them are overseas students (two from India through the ERASMUS-MUNDUS program at the UPMC, and another from Colombia). Similarly, over the past couple of years, former Team 14 has trained M2 students from abroad [Algeria, Spain (Erasmus program), Brazil and Argentina] and Argentinian junior scientists through the ECOS-Sud and INSERM-CONICET programs. The new Team (Team 11 in the report) will reinforce this politics, in particular in developing an attractive and updated website. Indeed, as pointed out by the experts, the website could be largely improved, although we would like to mention that the homepage of the team on the CRC website is kept updated, with pages on publications, current scientific interests and team members

available both in French and English. Making this new website available at the beginning of 2014 will be one of the first priorities of the new Team. Some of the members of the Team have already a strong expertise in scientific communication to large audiences, which will make it possible to develop an attractive website for young scientists abroad.

Last, we would like to stress that the new Team will pursue the in-house training of young scientists as it has been done for many years in the past by organizing weekly journal clubs and lab meetings (in English). These meetings will continue to be co-organized with former Team 10 (8 in the report, Dr. V. Frémeaux-Bacchi) and former Team 15 (12 in the report, Dr. J. Galon) to insure maximal scientific exchange. Also, scientific meetings that will be organized in the Department will help us to develop new collaborative projects with other Teams of the Cordeliers Research Centre.

Team N°13: Immunopathology and therapeutic immunointervention (Sébastien Lacroix-Desmazes and Srinivas Kaveri)

We would like to thank the Committee for the positive report on our activity and project.

We would just like to stress a number of points that do not appear in the report:

- Among the paper that we have published, there is one comment published in Nature, several editorials published in the N Engl J Med, a review in PLOS pathog, a paper in J Allergy Clin Immunol.

- We have obtained 6 ANR, one EU project and 3 grants from international agencies.

- The team members are either Organizers or Organizing Committee Members of several international symposia and meetings.

- Team members are Editors of journals: PLoS ONE; Scientific Reports , members of Editorial Boards: Immunotherapy, Cell Mol Immunol.

The Team has established an “International Associated Laboratory (LIA) at Mumbai, India, an initiative between INSERM and the Indian Council of Medical Research.

Team N° 15 : Cell death and drug resistance in lymphoproliferative disorders (Santos A. Susin)

Our team is very grateful to the members of the AERES Committee for the positive comments about our team. We are pleased to learn that the Committee saw the value of the team, the team leader, and the research program developed by our group at the Cordeliers Centre, making comments such as: ”team 19 has produced very interesting results on caspase-independent cell death, and the results that are produced can be trusted”, “The projects that will be pursued in the following years are of key interest “, ‘”The team leader is able to attract good PhD students and post-docs”, “Excellent integration of clinicians in the team”, “Good network of collaborations (national and international)” or “The team has been successful at raising funds”. Along with these constructive comments, the Committee raised two weaknesses that we propose to clarify:

1.- “The group needs to acquire a better international visibility”. “There is a discrepancy between the quality of the data produced by the team and the international visibility of the team leader”.

We fully agree with the Committee that our presence (and the presence of the team leader) in a more important number of international congresses should be increased. However, we would like to point out that the members of the team participated in at least two congresses on caspase-independent cell death per year and, as indicated by the Committee in the report, the clinicians of the team “have been invited to participate in a substantial number of national and international symposia”. The participation in these congresses has been certainly critical to establish a relevant number of international collaborations and European networks in chronic lymphocytic leukemia and in caspase-independent cell death (e.g., M. Sarfati in Canada for the assessment of CD47-mediated caspase-independent cell death or I. Miggeote in Belgium for the embryonic analysis of the AIF mouse model). The international visibility of Dr. Santos A. Susin is also corroborated by the recruitment, during the evaluation period, of five foreign PhD students, two European postdocs, and two Erasmus students. Indeed, Dr. Susin has recruited more than 80 % of the students/postdocs of the team. Finally, the participation of our team leader in national meetings has also contributed to creating networks that, coordinated by Dr. Susin, represent more that 67 % of the funds obtained by the team (1.981 out of 2.944 M€).

2.- “The team has very few collaborations with other teams of the CRC”

It is important to underline that our team, initially consisting of only 8 people, became part of the Cordeliers Center in April 2009 (at the middle of the evaluation period). Therefore, the number of internal collaborations is indeed lower than that of older teams, some of which have worked together for almost 20 years. In spite of that, we have already carried out strong and productive collaborations (including published papers) with: (i) C Sautes-Fridman/Sylvain Fisson (former Team 13). Primary intraocular B-cell lymphoma; (ii) JL Teillaud (Former Team 14). Anti-CD20 studies; and (iii) S Lacroix-Desmazes (Forer Team 16). Catalytic antibodies in splenic marginal zone lymphoma.

We are also currently developing different projects with other teams of the Centre. More precisely, we are working with: (i) Dr Alicia Torriglia (former Team 17) on our AIF mutated mouse model in order to understand the eye development defects associated with AIF; (ii) We are also studying the mitochondria structure alterations associated to this AIF mutant. This is done by an electron microscopy assessment performed by Danielle Chateau and Kevin Garbin (Team 4); (iii) We have recently helped Dr Cécile Guichard and Isabelle Hainault (former Team 8) to establish rat bone marrow derived macrophages and to verify their purity by FACS immunostaining. Finally, we occasionally interact with Team 1 or former Team 16 for exchange of protocols and advice.

Even if we agree with the Committee in that “novel opportunities for synergies exist in the new CRC project”, we would like to respectfully clarify that our team’s collaborations since 2009 demonstrate that we are well integrated in the Cordeliers Centre.

Team N° 16 : Information Sciences to support Personalized Medicine (Anita Burgun)

We thank the AERES committee for its positive conclusions. We would like to underline the following points :

1. As the committee stated, "*the field is very competitive*." Since the end of January, two of our articles have been accepted by JAMIA; one as first author, the other one as both first and last authors, and we submitted recently a paper on a Phenome Wide Association Study. We organized two workshops that will take place in Paris in May, one with the Vanderbilt group, and one with researchers from Kings College London to collaborate on our field. Moreover, P. Avillach, PHU in our group, will spend one year in Harvard (I. Kohane) starting 1st June 2013 in the team that has developed i2b2.

2. "*It could be useful to explore the possibility of developing personalized medicine in other public health relevant fields such as cardiometabolic diseases or mental health."*
   We have been working together only since September 2012, which corresponds to the arrival of A.Burgun, the team leader; yet, many projects arose with teams working on cancer research in the CARPEM project. We will develop further collaboration within CRC. Moreover, our participation in the IMI EMIF project gives us the opportunity to work in other public health fields. The EMIF General Assembly, which took place on March 1st, decided that the platform we are working on would be used for the medical EMIF axes, namely metabolic diseases, and Alzheimer's Disease. As such we are going to be involved in research work in medical fields outside cancer.

3. "*Team 22 would be strengthened if more people educated and experienced in epidemiology, more specifically in genetic epidemiology of complex diseases*."
   We have focused until now on CRC and hospital patient data sets. We recently performed a Phenome Wide Association Study, which is -- to our knowledge-- the first PheWAS conducted in France. The study is based on the HEGP data warehouse, which includes more than 600,000 patients. Our next step would be to extend our research to the population level. To achieve that goal, we are planning to recruit an epidemiologist. At the present time, we are involved in three master programs in Paris, which will help us for recruiting a genetic epidemiologist.