IPBS - Institut de pharmacologie et biologie structurale de Toulouse

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit :

Institut de Pharmacologie et de Biologie Structurale

From the :

CNRS

Université Paul Sabatier (Toulouse 3)

May 2010

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

Section des Unités de recherche

AERES report on the research unit

Institut de Pharmacologie et de Biologie structurale

From the

CNRS

Université Paul Sabatier (Toulouse 3)

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

May 2010

Research Unit

Name of the research unit : Institut de Pharmacologie et de Biologie Structurale

Requested label : UMR CNRS

N° in the case of renewal : UMR 5089

Name of the director : Mr Jean Philippe GIRARD

Members of the review committee

Committee chairman:

Mr Philippe SANSONNETTI, INSERM, Parisn, France

Other committee members

Mr Jacques POUYSSEGUR, Université de Nice, France

Mr Andrès AGUILERA, Université de Séville, Espagne

Mr Roland KANAAR, Erasmus University, Rotterdam, Pays-Bas

Mr Martin SCHEFFNER, University of Konstanz, Allemagne

Mr Joachim SEELIG, University of Basel, Suisse

Mr Marc BALDUS, Utrecht University, Pays-Bas

Mr Rafael MALDONADO, University of Pompeu Fabra, Espagne

Mr Salem CHOUAIB, Inserm, IGR, Paris, France

Mr David RUSSELL, Cornell University, Ithaca, New-York

Mr Matthias GUNZER, Otto-von-Guericke University, Allemagne

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

Mr Yves MELY, CoNRS member

Mr Laurent MARTINY, CNU member

Observers

AERES scientific advisor

Mrs Catherine DARGEMONT

University, School and Research Organization representatives

Mr Thierry MEINNEL, CNRS

Mrs Florence NOBLE, CNRS

Mrs Carine DESAULTY, CNRS

1 • Introduction

- Date and execution of the visit :

The site visit was conducted at once, by the group of experts, from Dec. 14 to 16, 2009 . This visit had been very carefully prepared by the Director, Jean-Philippe Girard and members of IPBS. The support documents were clear and concise and had been distributed well in advance, thus allowing optimal preparation of the visit. All necessary help and information was provided during the visit which was carried out in an excellent ambiance.

- History and geographical location of the unit and brief description of its field of study and activities :

IPBS was founded in 1996 with the aim to apply modern approaches of molecular, cellular and structural biology to the study of pharmacology, including, on these bases, the identification of new therapeutic targets and design of novel drugs. From its onset, IPBS was positioned on a fundamental basis with the permanent concern, however, to apply its research to the development of innovative pharmacological approaches. The current building that was inaugurated in Dec. 1997, is located on the CNRS 205 campus, Route de Narbonne in Toulouse. It is at the heart of the campus of Université Paul Sabatier. Its three major disciplines of interest are cancer biology, structural biochemistry-biophysics, and pathogenesis of mycobacterial infections with a particular focus on complex lipids that form the mycobacterial cell wall.

- Management team :

IPBS is organized in three departments: "cancer biology", "structural biology-biophysics", and "molecular mechanisms of mycobacterial infections". The new director, Jean-Philippe Girard is assisted by a CODIR that comprises the head of departments.

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	37	33
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	56	54
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	28	17 *
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	58,3	56,8
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	11	3**
N6: Number of Ph.D. students (Form 2.7 of the application file)	43	25,5
N7: Number of staff members with a HDR or a similar grade	57	53

* difference (5 more) with our "SV-UMR5089-JPGirard-3.5-Projetformulaire-S2-10-09-09.xls" table 2.4 (see pdf file attached – Conte, Mari, Mourgues, Paganin and Wasungu).

** not indicated in september in "SV-UMR5089-JPGirard-3.5-Projetformulaire-S2-10-09-09.xls" table 2.6 (Karine Rattier, Ségolène Galandrin, Thomas Prudhomme).

2 • Overall appreciation on the research unit

- Summary :

The panel wishes to stress the global scientific quality and ambition of IPBS. Under the new leadership of Jean-Philippe Girard, this institute plays an important role amongst the scientific community in Toulouse by bringing very basic and high-calibre approaches in cancer, structural biology, and infectious diseases research. In a very moving local situation marked by the development of a « canceropole » and an « infectiopole » that are expected to foster translational research in medicine, it maintains a strong pole of basic sciences that can generate original ideas, support on-the-edge, internationally competitive projects, assume high level teaching and training of students in basic disciplines, maintain high profile, up to date, technological platforms, and produce intellectual property that facilitates translation of the projects to biotech companies and bigger pharmas. The three departments, as they have been recently reorganized (i.e. Cancer Biology, Structural Biology-Biophysics, and Molecular Mechanisms of Mycobacterial Infections) create a new dynamics for this institute. IPBS thus stands as an original and essential structure in the French scientific community and appears irreplaceable in its basic approach of pharmacology and capacity to lay proper conditions for the development of novel therapeutic approaches in cancer and infection.

- Strenghts and opportunities :

The strengths of IPBS reside in the quality of its scientific staff, and capacity, over the years, to maintain a tradition of cutting-edge basic research in original topics that happen to be of increasing importance in medicine; in its ability to mobilize the human and financial resources required to establish state of the art technological platforms that are relevant to the questions addressed, and central to a network of academic and industrial collaborations in the Toulouse area (i.e.: proteomics, imaging, high throughput screening, animal facilities and transgenesis); and in its sustained efforts to maintain a strong integration with Université Paul Sabatier that makes it a keystone in the teaching and training of students.

Based on this original integration, IPBS is able to tackle ambitious scientific challenges. This is particularly the case for the study of DNA replication and transcriptions and its errors that lead to the loss of cellular homeostatic mechanisms in cancer, for structural and biophysical studies on membrane proteins that impact on the understanding of basic principles of channel functions in pharmacology, and for the study of mycobacterial lipids, a unique expertise available at IPBS, these compounds being key effectors of the chronicity of *Mycobacterium tuberculosis* infection. The basic approach applied to these domains warrants key discoveries and strong intellectual property that should foster the development of diagnostic tools and novel drugs for the treatment and prevention of cancer and tuberculosis.

The scheme seems perfectly adequate if one considers how successful IPBS is in securing funding from national and international agencies, including the European Union, and from contracts with industry. The same applies for the training of students and post-doctoral scientists who, with the junior staff members, stressed their appreciation of the scientific standards and the appealing value of the scientific platforms. All this results in a quite impressive scientific output in general published in the good specialty journals of the disciplines represented, as well as sometimes in journal of much larger audience and impact.

Possibly the most important issue is the opportunity to capitalize on the “good health” of IPBS to develop an ambitious policy of recruitment of high level young group leaders in its key disciplines that will warrant a bright future.

- Weaknesses and threats :

There was a general consensus among the panel experts that IPBS did not reach the level of national and international recognition and visibility it deserves with regards to the relevance of the topics addressed and the general quality of the scientific output. Even though progress is obvious over the last five years, markers remain that reflect a certain degree of self-effacement: i.e., little number of foreign post-doctoral trainees, limited attendance of the PIs and their younger colleagues to international meetings, the limited number of papers published in journals of broad audience and high impact factor. Some teams are doing better than others in this regard, but globally there is ample space for improvement of these markers, and for induction of a virtuous circle that would lead to attract the best young investigators from all horizons.

There was also a consensus on the fact that the exploitation of the multi-disciplinarity available at IPBS was suboptimal in its capacity to generate novel research topics at the interface of disciplines. Strong collaborations exist inside Departments, but little is occurring otherwise with the exception of projects involving structural approaches.

Last but not least, a clear defect was observed in technical support. The development of cutting edge platforms has rightly drawn several positions of engineers and technicians to fill these essential needs. This however has occurred at the cost of some of the teams benefiting of no technical support. This point was stressed by all categories of scientists and the risks associated to it were emphasized, particularly regarding the future of animal facilities.

The panel did not identify major threats, although the two points raised above may be a matter of concern for the development of IPBS if not seriously taken into account.

- Recommendations to the head of the research unit :

The panel recommends that maximum efforts be made at all levels, particularly the Direction, heads of departments and PIs, to improve the visibility of IPBS outside. This may involve several tools:

- Aggressive recruitment of new group leaders thanks to the assembly of attractive packages and clear evidence of continuous support.
- More active participation to international presentations (meetings, seminars, etc…);
- Global effort to publish important discoveries in the best possible journals.
- Support to investigators to apply to international competitions like the European Research Council.
- More active lobbying to get scientists of IPBS to occupy visible positions in national and international institutions (i.e. scientific awards, Academies, EMBO, etc…).

The President of Université Paul Sabatier, in his intervention, reaffirmed his strong support to IPBS, and confirmed his commitment to provide optimal support regarding the necessary positions of technicians, the relief of some teaching burden from "enseignants-chercheurs" to dedicate more of their time to research, and his interest in supporting recruitment of outstanding young investigators.

- Production results :

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	84
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	32
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	0,96
A4: Number of HDR granted during the past 4 years	14
A5: Number of PhD granted during the past 4 years	66

3 • Specific comments on the research unit

- Appreciation on the results:

It is very relevant to have such a high quality institute in this environment, the research is for the most part original, impact is mixed however. Internal integration is very good, attested by the number of joint publications. The panel recognized a good number of publications, although of variable level, from good to excellent. Compared to the potential, this marker could be improved.

A partnership with industry is very well engaged. IPBS is an essential component for the future of translationnal research in Toulouse.

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

The panel noticed a very low number of awards. This marker should also be improved.

The panel also noticed a very low level of recruitment of foreigners. On the other hand, recruitment of young group leaders has been good.

IPBS teams are good at raising competitive fundings (national and international) although EU funding could be improved.

The panel noticed that collaborations with foreign groups is highly variable.

There is a good number of patents, and a good relationships with companies.

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

A collegial type of direction is implemented by the new director. IPBS members feel satisfied in general. Information can be still improved. The Website has to be improved (english version). Communication has to be more professional.

The Graduate students were extremely positive about their experience at IPBS. They felt that there were sufficient opportunities to expand their expertise, practice their presentation skills, and add to their non-scientific knowledge. Most of the students were recruited locally or through direct interaction with faculty rather than to the Program at the IPBS indicating that the visibility of the Institute could be increased to enhance recruitment globally. One panel member raised the issue of ethical formation of students beyond the mere aspects of animal experimentation (i.e.: ethics of scientific publication).

Post-doctoral and permanent scientists: This group had met three times in preparation of its discussion with the AERES panel, thus expressed a series of well thought about points regarding IPBS. They praised the global quality of the institute, particularly the dedication and efficiency of the administrative and technical teams (i.e. ordering and delivery of consumables), and the support offered to the newcomers upon their arrival on the site. They also praised the high quality, accessibility and training value of the technical platforms. They also stressed the importance of these platforms in the visibility of IPBS outside, particularly for possible post docs. The group also expressed a certain number of remarks and suggestions which, in general, reflected its strong attachment to the institution. The major one was about communication, both inside and outside. They consider that communication of IPBS to the exterior is suboptimal and that additional efforts should be invested into improving the web site (including a version in English) to make it more attractive and reflective of the ongoing science, particularly its most visible achievements, and of the technological platforms. They also stressed the need for the group leaders to be more present on the international scene. Post-doctoral trainees insisted on the fact that an attractive web site, a good seminar in a foreign University/Institute are very important criteria, on the top of the publications level to decide upon selecting a laboratory for a post-doctoral training.

Internal scientific communication was considered satisfactory in general, One complaint was about the lack of a common place where scientists of the three departments could meet and socialize. The multidisciplinarity of IPBS is a strength and all efforts should be made to increase the chances of interaction between the scientists from the three departments. The group finally stressed the fact that the communication between the Direction of IPBS and researchers had improved but was not yet optimal.

In addition to communication, three issues were raised that may need global discussion and consensus at all levels of IPBS:

- The possibility for non group leaders to apply for their own grants. This seems to be a sensitive issue in some groups, thus the need to openly address the issue.
- The position of scientists in papers, particularly when a group leader, a permanent staff scientist, and a post-doctoral/student are involved. This, as in many other institution poses the problem of the scientific independence of the permanent staff scientists who have not reached the status of group leader, and its expression and recognition. This seems also to be an issue that should be openly discussed.
- The lack of stable positions of technicians in some groups, and the possibility to consider positions of lab managers to relieve a lot of the burden of ordering consumables and other items.

Technicians, engineers, administrative staff; the participants were in general happy with the formation offered to improve their respective expertise.

On the other hand, a certain number of concerns were expressed including:

- The fact that too much personnel is hired under a temporary contract (CDD). More permanent positions should be offered to achieve the sustainability of expertise.
- Special attention is requested regarding the follow up of their careers. It was proposed to consider the creation of a position of human resource director (DRH) at IPBS.
- The balance in the distribution of technical and engineer positions to the different team should be improved, and decided according to the size and competitiveness of the team.
- One way to proceed would be to redirect some positions of technicians from the University to IPBS.
- The panel decided to reproduce these elements in extenso because regardless of their professional category, all personnel had made a strong collective effort to identify possible problems and suggest constructive solutions, which proved extremely valuable for the panel members.
- Relevance of the initiatives aiming at the scientific animation and at the emergence of cutting edge projects : The panel suggests to strengthen Internal (transdepartmental) collaborations to make maximum profit of the interdisciplinarity available at IPBS. The management of IPBS has initiated a scientific animation policy (special days, “Prestige day” with renowned invited speakers…). This initiative has to be encouraged. The participation of IPBS scientists to international meetings should be improved.
- Contribution of the research unit staff members to teaching and to the structuration of the research at the local level : The panel recognized a very good participation to teaching. It also recognized the major efforts invested in IPBS structuration through the platforms, and this was seen as a remarkable achievement.

- Appreciation on the project :

Existence, relevance and feasability of a long term (4 years) scientific project : The reorganization of IPBS departments allows new and interdisciplinary projects and creates a new dynamics.

Existence and relevance of a policy for the allocation of ressources : A good policy for big equipments funding was noted. Allocation of technical support to platforms is in general adequate. However, the absence of a stringent ressources allocation policy was noted. As a matter of fact, a large part of the funding is obtained by the various units on competitive grants.

Originality and existence of cutting edge projects : There are cutting-edge projects in each department (Interface between cell biology and mycobacterial lipids, biophysics on membrane proteins, HEV). A continuity has been noted for the strong research lines existing at IPBS, and for the maintenance and development of specific expertises (lipids…).

4 • Appreciation team by team and/or project by project

Name of the team : E1 – "Microenvironment, Cancer and Adipocytes"

Name of team leader : Mrs Catherine MULLER-STAUMONT

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	*	
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0,8	1,8
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	2
N7: Number of staff members with a HDR or a similar grade	1	2

NB: Martha Dabek, polish postdoctoral fellow, BQR UPS, will work in the team from 01/09/09 until 21/08/10.

- Appreciation on the results :
  - This team has pursued an interesting project on hypoxia and DNA repair. Particularly interesting is the discovery of PI3KK in the activation of the HIF pathway. A new project is conducted in collaboration with an expert in obesity and associated pathologies, in particular breast cancer (Inserm, Toulouse). This is a particularly innovative program devoted to demonstrate the implication of cancer associated adipocytes in tumor progression. The preliminary results on the cross talk between adipocytes and tumor cells support this new hypothesis and point to the impact of adipocytes on tumor invasion.
  - The team has published 11 papers in the last 4 years in specialized journals (on DNA repair project). 1 paper and one review appeared on the new project.

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

The attractiveness of this team that was created in 2008 could be improved. Many invitations to local and national scientific manifestations which has to be expanded to the international level. The ability to recruit top-level researchers, post-doctoral and other students, especially foreigners needs to be improved. The team was successful in obtaining several grants from charities, industry and national agencies. This team has important collaborations but only at national level.

- Appreciation on the project :

The committee has no particular objections in regard to the feasability of the project but it recommends to restrict the number of questions addressed by the team.

- Conclusion :

— Summary :

The committee believes that this team is conducting a very original project in the field of tumor microenvironment. The understanding of the role of adipocytes in shaping the stroma is of fundamental value and could have potential clinical implications.

— Strengths and opportunities :

This initiated collaborative project is indeed a good opportunity for this young team.

— Weaknesses and threats :

Major weakness is related to the limited size of the team and lack of full time senior researchers.

— Recommendations :

Focus on competitive aspects of the project and recruit additional full-time researchers.

Name of the team : E2 – "High endothelial venules (HEVs), Inflamation and Cancer"

Name of team leader : Mr J-P. GIRARD

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1,5	1,5
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	2
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results:

This team has initiated 15 years ago a project based on the Biology of specialized High endothelial venules (HEV) and their involvement in inflammation and cancer. The project is expanding in 4 specific areas with a major goal being to identify the signalling leading to the induction or repression of the HEV functional phenotype. Advances that could be made in this field will lead to the control of lymphocyte recruitment in normal and pathophysiological situations.

This team is taking advantage of cutting edge technologies (imaging, functional genomics and proteomics, transgenic mice, structural biology). This team produced 14 publications, 2 patents - The results obtained by this team were published in good impact factor journals (PNAS, Blood, EMBO R). 5 theses were defended.

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

The team is involved in several international collaborations (European network of Excellence and International Regulome consortium) as well as in several national networks. In regard to the scientific excellence of the team, invitations to international meetings has to be improved. Its ability to recruit top-level researchers, post-doctoral and other students, especially foreigners is good. Success in getting funding from several agencies is excellent. The team is constantly supported by the French Ligue since 2003 and has good interaction with pharmaceutical industries. The team has outstanding participation in international or national programmes, as well as important collaborations with foreign teams.

- Appreciation on the project:

Based on the originality, the focus on four well identified objectives, the committee is highly confident on the success of this project. As pointed out above, this competitive team is conducting an outstanding research and has identified a specific niche (HEV, IL-33, THAP1) that has resulted in original findings.

- Conclusion:

— Summary :

This is clearly an outstanding team with high originality, performance and strong integration with the Institute platforms and facilities. The committee was impressed by the scientific strategy and vision of the team leader.

— Strengths and opportunities :

The panel stressed the originality of the project and specificity of the niche enriched over the last 10 years by the group leader.

— Weaknesses and threats :

The panel noted a lack of international visibity of the team.

— Recommendations :

To urgently increase international visibility and group size.

Name of the team : E3 – "Sphingosine 1-phosphate as a therapeutic target in cancer"

Name of team leader : Mr O. CUVILLIER

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	2*	1
N7: Number of staff members with a HDR or a similar grade	3	3

* included Ke Zheng, chinese Ph.D. student, present in laboratory for a training period from october 2008 to september 2009.

- Appreciation on the results:

The role of sphingolipids and in particular sphingosine-1-phosphate (S1P) and Sphingosine kinase-1 (SphK1) represents an emerging field in basic and applied cancer research. Although the team leader has not made much effort to put his research into a broader context (in particular with respect to data from other groups), it is evident that the team made significant contributions to the characterization and validation of SphK1 as a potential target in the treatment of certain cancer entities. Thus, quality and impact can be considered as high. The team published 9 original manuscripts, 3 reviews and one book chapter. Considering the size of the group, this can be considered as good (with respect to quantity), as all of the manuscript were senior-authored by the team. The quality of the publications is fine with 4 manuscript published in leading cancer journals (Cancer Res, Leukemia). Furthermore, the team was involved in the generation of two books for the public on prostate cancer, which indicates the standing of the team in cancer research in France. Finally, 4 PhD theses were completed.

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

Only a few invitations (3) to international conferences are mentioned. There is certainly room for improvement. In the new project period, there is one new researcher at the CR1 level in the group. At present, there is only one graduate student in the team.

The team attracted a number of grants from charities, industry and public bodies. The team appears to be reasonably well connected at the international and national level but does not appear to be involved in any programs such as EC consortia. As indicated, there is potential for application of the reagents produced/studied and the results obtained and, thus, the project has socio-economic potential.

- Appreciation on the project :

The projects (role of S1P in intratumoral hypoxia, metastasis of prostate cancer cells, S1P lyase in prostate cancer, clinical studies) are a logical continuation of the previous period and are certainly relevant to cancer research. Based on the record of the team, it can be expected that interesting results will be obtained that can be published in leading cancer journals.

As indicated above, the projects are original and there is no doubt that the studies will be performed with success. However, it will be important to provide strong evidence that S1P metabolism indeed represents a promising target for the development of new anti-cancer strategies.

- Conclusion :

— Summary :

This is an interesting project that addresses an important question of cancer research. The link to clinical research and to application is clearly provided.

— Strengths and opportunities :

The team has a long-standing expertise in this research area. The SphK1 field is still a rather young field (i.e. not overly competitive yet) and, thus, the team can place itself as one of the leaders in the field, particularly with the strong cooperation with clinicians.

— Weaknesses and threats :

The proposed projects remain at a descriptive level, i.e. no efforts are made to identify the mechanisms by which S1P affects cancer cell metabolism at the molecular level. Such studies would be important to solidify the notion that SphK1 (or other components involved in S1P metabolism) may represent a therapeutic target.

— Recommendations :

The panel advised to establish closer interactions with team E1.

Name of the team : E4 – "Targeting of proteins to proteasome in cell differentiation"

Name of team leaders : Mr Pierre LUTZ – Mrs Christel MOOG-LUTZ

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results:

The main topic of the group is the role of the ubiquitin-proteasome system in hematopoiesis and in muscle cell differentiation, with a particular emphasis on Asb2, as the team leader has shown that this protein represents the substrate recognition component of a Cul5 ubiquitin ligase complex. The team joined the IPBS in 2006 and since then, has made original contributions to the characterization of Asb2 and its potential involvement in leukemia. The project can be classified as basic cancer research (as deregulated protein degradation is frequently observed in various cancer entities). Whether or not Asb2 and its substrates may represent potential targets for anti-cancer approaches remains to be elucidated in the future. Since the arrival of the team leader, the group published 6 original manuscripts and 1 review. At first glance, this is not overly impressive but considering that 5 of 6 of the manuscripts were published in the past two years in internationally recognized journals, quantity and quality can be considered as good. One thesis of high quality was finished in the reporting period.

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

The abovementioned thesis was awarded a prize of the ARC. The team leader was invited to 3 international conferences indicating that his research is recognized in the respective field. In the new period, two permanent researchers will join the team. There is only one graduate student in the team. Team leader is a recipient of the ANR young investigator program. Furthermore, the team attracted several grants from charities and public funding bodies. The team appears to be reasonably well connected on the international and national level but does not appear to be involved in any programs such as EC consortia. As indicated above, on the long term the research may identify potential targets for anti-cancer strategies.

- Assessment of the strategy, governance and life of the team or project:

One member (university professor) is involved in teaching and in a local scientific committee.

- Appreciation on the project :

The projects (role of Asb2 in hematopoiesis and muscle differentiation; mechanisms of action of Asb2 proteins) are a logical continuation of the previous period and are likely to produce results that can be published in internationally recognized journals. However, the generation of respective mouse models appear to be of major importance for the success of the project.

As indicated above, the eventual relevance for basic and, in particular, applied cancer research remains to be proven. Asb2 proteins are only poorly characterized. Thus, the proposed projects are certainly original. Furthermore, there are only a very few groups worldwide working on Asb2 proteins. This is an important issue in an otherwise highly competitive research area (ubiquitin-proteasome system).

- Conclusion:

  — Summary:

The panel considered the project to be good, with reachable goals.

  — Strengths and opportunities:

Not many groups are working on Asb2. Thus, by thoroughly characterizing Asb2 and its role in hematopoiesis and muscle differentiation, the team can place itself at a competitive position in the field. Furthermore, the close collaboration with the Proteomics group is a major asset for the project.

The assumption that by determining protein expression levels at the proteome level, direct substrates of Asb2 can be identified appears to be somewhat naive. Similarly, it remains to be shown that large scale in vitro ubiquitination assays are indeed suited (for a small group) to identify substrates.

  — Recommendations:

The panel advises the team to pay close attention to the feasibility of some of the key approaches with regards to the means available and the strategy selected.

Name of the team : E5 – "Genotoxicology"

Name of team leader : Mr Giuseppe VILLANI (E6 in the scientific report – Mrs Martine DEFAIS)

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	
N7: Number of staff members with a HDR or a similar grade	3	3

- Appreciation on the results :

Overall, the committee rate this research team as very good. They have pursued four projects.

The first project analyzed the interaction of gamma-tubulin and RAD51. However, the relevance of this interaction and the mono-ubiquination of gamma tubulin for recombination and repair still needs to be clarified.

The second project analyzed molecular mechanisms of replication of damaged DNA. This is the most extensive of the team's projects and consist of three subprojects. First, they analyzed replication of a template with an abasic site by the bacteriophage T4 replicative complex and found that the proofreading activity and auxillary proteins of the polymerase play an important role in bypass of the damage. Second, they analyzed the role of the Herpes simplex virus UL2 protein (a uracil-DNA-glycosylase) on UL30 mediated replication of uracil containing DNA. In the third subproject the characterize the properties ofthe human TLS polymerase lambda and auxillary proteins such as RPA and PCNA in replication of damaged templates. All three subproject are designed to answer important mechanistic questions concerning the replication of damaged DNA templates and have an imporant impact.

The third project aimed to explore the relationship between replication and recombination of damaged DNA. Here the participants analyzed DNA strand exchange in vitro by E. coli RecA on DNA substrates containing an intrastrand cis-Pt crosslink. The experiment described in the report as actually a bit removed from the message in the title. It may be solid work, but its impact remains to be made clear.

The fourth project is the investigation of protein-DNA interactions using a technique developed by the project leader. The technique allows recording of the CD spectrum of a particular base in a protein-DNA complex and thereby obtaining information on the conformation of the base in the complex. The technique has been applied to N protein of phage lambda and an RNA hairpin and they have begun to apply it to DNA polymerases and primer template junctions.

The team has 21 publications in solid peer reviewed journal. Many papers are in J. Biol. Chem. and Nucleic Acids Res., which are very good journals. The highlight is a co-authored publication in Nature. One thesis was produced. There are not many oral presentations of the work (7 are listed) and but only one has been abroad.

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

No awards are listed in the report. As mentioned above there appears to be only one communication at an international conference. The ability to recruit high level scientists, postdocs and students from abroad is low and therefore it is a weakness of the team.The team has seven small national grants, including two with industry. Its largest grant is an international grant from the NIH (USA) for a three year post-doctoral fellow salary. There is no evidence of participation in networks in the report. The team does, however, list a number of national and international collaborators. The international collaborators are of high level in the fields of biophysical chemistry and replication. This team has a low participation in teaching.

- Appreciation on the project :

The overall goal of the team in the next four years is to analyze molecular mechanisms of replication of damaged DNA templates by replicative DNA polymerase complexes. They will analyze complexes involved in replication of bacteriophage, eukaryotic viral and human DNA. The experiments are firmly based on solid results from the previous years and exploit newly designed replication templates containing DNA damage. The team proposes five projects. They want to explore [1] how auxilliary proteins work to result in lesion by pass of an exo- bacteriophage T4 replicative complex; [2] how DNA helicases such as the MCM complex and the Werner protein, support human polymerase complex in replicating damaged fork-like DNA substrates ; [3] how the uracil DNA glycosylase UL2 of Herpes simplex virus effect replication kinetcs and fidelity of HSV-1 DNA polymerase (UL30) and processivity factor (UL42) ; [4] how, using a new structural technique that the team developed, DNA polymerases perform the initial base selection step ; [5] how to use Ruthenium complexes to photochemically inhibit DNA polymerase activity to eventually lead to novel antiviral and antitumor therapies. The projects are solid and should lead to further mechanistic insight.

The proposed project are very good and represent very solid science that will provide new mechanistic insight into how certain damaged DNA templates can be replicated.

- Conclusion :

— Summary :

This team has a good track record and refocusses on its strongest theme. The team has the potential to be more productive in the future provided that they create more international visibility.

— Strengths and opportunities :

The team is poised to exploit a newly developed unique assay to understand proofreading in DNA replication reactions. High-quality collaborations with top researchers in the field. Clear objectives and high biochemical skills.

— Weaknesses and threats :

The panel noticed difficulties in recruiting new students, and a low international visibility that does not correspond to the quality and relevance of the work performed.

— Recommendations :

The panel encourages the team to find ways to increase the number of students and young researchers in the group, e.g. by increasing the visibility of the group at international meetings. Also more attention should be paid to authorship positions on collaborative papers.

Name of the team : E6 – "Radiobiology and DNA repair"

Name of team leader : Mr Patrick CALSOU (E7 in the scientific report – Mr Bernard SALLES)

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)		
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2,3	0,5
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.7 of the application file)	3 *	
N7: Number of staff members with a HDR or a similar grade	3	3

* included Qiao Cheng, chinese Ph.D. student, present in laboratory for a training period from october 2008 to december 2009

- Appreciation on the results:

Results from three research lines are presented in the report. The first project involves analysis of the NHEJ pathway in cells that is required for repair of radiation induced DSBs. The team analyzed recruitment of proteins in this pathway to localized DNA damage. They mapped phosporylation sites on Ku and XRCC4, but the relevance of these sites for repair remained unclear. They analyzed a backup pathway for NHEJ and showed a role for PARP1 in this pathway.

Finally, found that Ku has roles in the membrane of cells as they found an iteraction of Ku with the metalloprotease MMP9 and identified that Ku is expressed on the cell surface of primary acute leukaemia cells. In the second project the team investigated external factors that influence the cellular response to radiation. They concentrated on cell differentiation and hypoxia. They showed that the NHEJ DSB repair activity appears to increase during adiocute development and that NHEJ factor DNA-PK controls HIF1alpha degradation. The third project is listed as translation research where they setup a microtiter plate assay to quantify the kinase activity of DNA-PK in response to plant extracts. No compounds were found. In this project they have also set up a comet assay to analyze blood samples from pesticide expose farmers. Presumably they want to measure DNA breaks, but it is not specified what kind of breaks and how long after pesticide exposure.

The team has 29 peer reviewed publication in solid journal with the highlights being 3 papers in Cancer Res., a paper in EMBO Rep. and a co-authored paper in EMBO J. Six PhD theses were produced, while the number of presentations at meeting was limited, with only one at an international meeting.

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

No awards are listed in the report. As for contributions to international conferences/seminars ; the new team leader has few.

The composition of the team suggests that this apect can be improved.

The team has two small grant with industry (EDF Radiobiology committee), six small national grants and one larger one (INCA Projects libres intracanceropoles). There are are no international grants.

The team has two international partners of solid reputation. There are five collaborations at the national level.

- Appreciation on the project

The main goal of this team is to understand the response of tumor cells to radiotherapeutic treatment. The theme of the team's future projects is repair of DSBs by NHEJ in human cells. There are three main projects each consisting of subprojects. The focus of project 1 is the DNA-PK dependent NHEJ pathway and in particular its mechanism of action, identification of new factors involved and potential pharmacological applications. The team has identified a new protein that is phosphorylated by DNA-PK and will investigate its role in NHEJ. They will also pursue experiments to analyze the role of phosphorylation of XRCC4 using techniques previously established by the team. In previous experiments the team has resolved the interaction between Ligase IV and XRCC4 at the atomic level and they will make use of this information to screen for compounds that disrupt this interaction and thereby might inhibit NHEJ. Finally the want to design compounds that mimic radiation in its ability to induce compound complex DNA damage. In project 2 they want to identify and characterize human proteins involved in alternative NHEJ. The alternative pathway of interest is Ku-independent and highly error prone. The have generated a cell line in which Ku can be done regulated and what to use this to identify proteins at sites of breaks in the absence of Ku that might represent proteins involved in the alternative Ku-independent pathway. This will be done by both cell biological (microscopy) and mass spectrometry based approaches. Project 3 is actually a collection of less related research lines. The teams want to investigate why Ku is essential in human cells, they want to test whether the alternative NHEJ pathway plays a role in telomere metabolism, define the role of BRCA1 in NHEJ and determine how cells in mitosis respond to DSBs. In summary, team proposed many projects that center around NHEJ and are certainly feasible and have the potential to be useful in exploiting NHEJ as a pathway to perturb the cellular response to ionizing radiation.

The team proposed a mix of projects that vary from more or less mainstream to original.

- Conclusion :

  - Summary :

This is a solid team with a new team leader for the coming period. The proposed projects are original and have the potential to be useful in anti-cancer treatments via radiotherapy. Good scientific production in which the new PI has been corresponding author. Group would benefit from obtaining international funding.

— Strengths and opportunities:

The team has a number of strong projects centered around NHEJ mechanisms which will make it internationally competitive. The team has a new leader with a convincing vision. The potential of the group to do high through put screening for inhibitors of NHEJ is important and a promising opportunity for cancer research.

— Weaknesses and threats :

The panel stressed a yet low international identity.

— Recommendations :

The panel encourages the team to raise its international funding. The PI should participate more in international meetings in the field of DNA repair.

Name of the team : E7 – "Genetic instability and transcription regulation"

Name of team leader : Mr Amine KHAMLICHI (E8 in the scientific report)

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	2 *
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	
N7: Number of staff members with a HDR or a similar grade	1	1

* NB : Caroline Conte, postdoctoral fellow, non indicated in our "SV-UMR5089-JPGirard-3.5-Projetformulaire-S2-10-09-09.xls" table 2.4, present in laboratory from novembre 2009.

- Appreciation on the results:

This PI started at IPBS three years ago. The team shows good quality and impact of the work. The main objectives of this team have been to understand the structural and functional parameters that regulate class switch recombination. Several publications have been produced on the stalling of RNAPII at Smu regions during somatic hypermutation and their relationship with chromatin and R-loop formation. They have generated a knock-in mouse line in which they inserted a chimeric transcription unit made out of the mouse Ialpha GL promoter/exon and an exon from human beta-globin. The achievements are reasonable and should lead the team to establish a solid line o research if they are able to diversify their approches and expand their goals.

The team has 10 publications in peer-reviewed journals, including one as last senior author in PNAS. It appears that the team has produced 4 thesis.

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

It is still at an early stage of his career. No invitations reported. Organizer of a local international meeting. Several national or regional grants with standard amounts of funds each. No international funds raised. The team has a number of very good international collaborators.

- Appreciation on the project :

The main objectives of this team have been to understand the structural and functional parameters that regulate class switch recombination. They plan to study long-range interactions during V(D)J recombination and allelic exclusion in the mouse IgH locus, as well as the effect of the 3' RR and GL promoters, the targeting of AID and the regulation of class switch recombination. They will pursue their studies on the co-transcriptional mechanisms that help AID targeting and class switch recombination. The project is realistic and deals with a very and hot competitive subject, due to its impact in the field of oncology and immunology, that could be exploited better in international context and for fund rasing. A diversification in the type of approaches would be beneficial.

The Unit maintains a number of international collaborations in the Immunology field, plus national networks and collaborations. Most of the PhD theses initiated are scheduled to finish 2010.

The PI got several grants with short amouns of funds but no International funds.

The theme of the proposed projects is original and overall the team's projects are promissing. It would benefit from additional experimental approaches, however.

- Conclusion :

— Summary :

This is a recently established team that has been able to make a number of relevant contributions. In the future, it should focus on engaging in new experimental approaches allowing internal collaborations and secure funding and group size to remain competitive.

— Strengths and opportunities :

The group has clear objectives, is well focused and has a strong expertise in mouse genetics. It shares good collaborations with top-researchers in the field.

— Weaknesses and threats :

The group may be too small to maintain an international competitiveness in a long term. It has a low degree of integration with other researchers within IPBS.

— Recommendations :

It would be helpful to engage in more immunological questions to allow productive internal collaborations within the IPBS. A diversification of experimental approaches would complement the current data. The PI should improve his international visibility and try to raise international funding.

Name of the team : E8 – "Transcription and DNA repair"

Name of team leader : Mrs Ambra GIGLIA-MARI (E9 in the scientific report)

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	2 *
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0,4	0,9 **
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	0,5 ***	1
N7: Number of staff members with a HDR or a similar grade		1 ****

* NB : Sophie Mourgues, postdoctoral fellow and Pierre-Olivier Mari, other researcher, non indicated in our "SV-UMR5089-JPGirard-3.5-Projetformulaire-S2-10-09-09.xls" table 2.4

** included Christine Bordier 50% in the team (and only 50 % in SC3)

*** Lara Kaddoum 50% in the team (and only 50% in E. Joly team, n° E18 scientific report)

**** Ambra Giglia-Mari HDR viva in decembre 2009, non indicated in our "SV-UMR5089-JPGirard-3.5-Projetformulaire-S2-10-09-09.xls" table 2.3

- Appreciation on the results:

This team started only recently (January 2009) and therefore the report only covers this year and the activity of the team leader as post-doctoral fellow from 2005. The team leader generated a ground breaking mouse model that carried a knockin allele of the XPB subunit of TFIIH which expresses the XPB protein fused to GFP. TFIIH is a central protein complex in both transcription and DNA repair via nucleotide excision repair. The team leader used this model to pioneer quantitative fluorescence measurements in live organotypic tissue slices, which allowed her for the first time to analyze the behavior of the important TFIIH complex in many different cell types. This exciting mouse model will be a pivotal research tool for her current and future independent research. The work is highly original and of excellent quality.

The team has 8 publications in peer-reviewed journals, including two first author ones in Plos Biol. And one in PNAS. This is very good for a team at this stage. Obviously, PhD dissertations have not yet been produced.

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

Even in this early stage of team leader's career, she already obtained an international grant from the Association of International Cancer Research (AICR). In addition, she has already obtained two national grants. Being this successful in fundraising at this early stage of her career demonstrates that the team leader masters this skill to perfection.

The team has a number of very good international collaborators. They multidisciplinary, ranging from chemists to biochemists and molecular biologists and leading in the field.

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

For a starting team leader, the size of the current team seems appropriate (Three post-doctoral researcher, a technician and a PhD student).

The team leader is committed to teaching.

- Appreciation on the project:

The team proposes a set of three related projects. They are all based on the cutting edge research tool that the team leader generated during her post-doctoral research period. Thus, the essential biological reagents for the proposed experiments are ready to go. The proposed projects are solid and will serve the team well to establish its position in the field. In the first project the team will follow up on their observation that the transcription/DNA repair factor TFIIH behaves differently at the cell biological level in post-mitotic versus proliferating cells. They will address the molecular mechanism of this observation using mass-spectroscopy analyses, analyses of post-translation modifications and ChIP experiments. The second project concerns TFIIH DNA repair activity in living tissues. The dynamics of TFIIH interaction with locally damaged DNA sites will be assessed by FRAP experiments. The team will be in a unique position to come the behavior of the protein in different (living) tissues. An important challenging aspect of this project is how to relate the cell biological observations to molecular function. The third project proposes to study the behavior of TFIIH in cells and tissues containing mutant forms of the TFIIH subunit obtained through mouse crosses. The mutations are mimics of those found in nucleotide excision repair deficient patients and might provide insight in how phenotypic differences, such as in premature aging and carcinogenesis, between patients is established. In summary, the team's projects are cutting edge and it is in a unique position to pursue them.

The theme of the proposed projects is highly original and overall the team's projects are cutting edge science.

- Conclusion :

— Summary :

This is an very promising new team, with a talented team leader. They have cutting edge projects to pursue with ready to go models. It keeps excellent international collaborations.

— Strengths and opportunities :

The knockin mouse model is a unique strength of this team offering them the opportunity to address important new research avenues. They have a keen sense of which questions to follow up and clear objectives, separated from the mainstream going on in a very competitive field. Excellent collaborations with top-researchers in the field.

— Weaknesses and threats :

The panel warns that long term plans propose more of the same current research(ie making more GFP knock-ins). Attention should be paid to better define long term objectives, particularly by introducing more biochemistry in the approaches.

— Recommendations :

The panel advises to strengthen biochemical approaches to probe mechanisms. This would be highly beneficial to enhance the competitive edge of this promising group.

Name of the team : E9 – "NMR and Protein – Membrane interactions"

Name of team leader : Mr Alain MILON (E11 in the scientific report)

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1,5	1,5
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	3,5	3
N7: Number of staff members with a HDR or a similar grade	3	3

- Appreciation on the results:

On the structural biology level, the team targets the structural characterization of membrane proteins and has already contributed by providing the structure of kpOmpA which represents a remarkable accomplishment. Furthermore, the group has made progress in establishing a promising research line on GPCRs. These proteins of outermost biological relevance. At the same time, they are well known to be difficult to produce and to structurally characterize. The group also has established a novel approach that uses NMR in combination with other biophysical methods to study structure and dynamics of membrane-embedded peptides.

The team uses extremely interesting tools that are very useful to collaborate with other teams of the Institute. The PI is coordinating an European Network joining some of the best European teams in biophysic and computation. A second topic is devoted to study the structure, dynamics and function of membrane proteins and includes the study of several interesting proteins, some of them in collaboration with other international teams. A third topic is devoted to the study of the structural biology of soluble proteins and includes very interesting collaborations with other teams of the Unit. In addition, the team has developed new softwares that have open new collaborations of interest.

— Number and quality of the publications, scientific communications, thesis and other outputs:

With an average number of more than 5 publications per year and several book contributions, the group quite productive. Many results have been published in internationally leading scientific journals of their specialty. They also have some few collaborative publications in high impact journals, mainly the PNAS published in 2007. Five Ph.D.s were granted in the reviewing period. There is also seems to be a strong link to industry and external funding, in particular to EU funding. The team has also registered some patents and has developed interesting sofwares.

— Quality and stability of partnerships :

The group seems to collaborate with internationally well known groups.

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

  — Number and reputation of the awards obtained by staff members, including invitations to international conferences and symposia:

The team has obtained an award from the French Academy of Science in 2005 and has a good record of invited conferences at national and european level (8 in total).

  — Ability to recruit high levels scientists, post-docs and students, and more particularly from abroad:

Two foreign PhD students, and 2 french ones are now included in the team. In addition, five Doctoral Thesis have been achieved in this four years period.

  — Ability to raise funds, to successfully apply for competitive funding, and to participate to scientific and industrial clusters:

The team has an excellent record of raising funds from national and international public agencies as well as from industrial partners. The PI is coordinator of an European Integrated Training Network.

  — Participation to international or national scientific networks, existence of stable collaborations with foreign partners:

The PI is coordinator of an European Integrated Training Network and has an excellent record of collaborations at the national and international level, including very interesting collaborations with other teams of the Unit.

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

The team is involved in several teaching activities in Toulouse. Two professors and one associate professor are included in the team.

- Appreciation on the project :

Research on membrane proteins is clearly of highest scientific caliber. The group has now all expertise in house to significantly contribute to the structural biology of membrane proteins in close collaboration with colleagues of the institute. The same applies to protein – DNA complexes. Importantly, they are also involved in developping novel biophysical approaches to takle challenging biomolecules.

- Conclusion :

  — Summary :

Excellent group with cutting edge projects.

  — Strengths and opportunities :

The platform and the scientific staff provide a very good environment to address cutting-edge projects in the various fields of structural biology. The team seems to be well connected within the institute. The PI and the group are visible on the international level.

  — Weaknesses and threats :

The GPCR project could perhaps benefit from exploring other reconstitution protocols and structural biology tools. The impact of the publications could be improved.

— Recommendations :

The group has everything in place to be more ambitious in targeting high-impact journals.

Name of the team : E10 – "Proteomics and mass spectrometry of biomolecules"

Name of team leaders : Mr Bernard Monsarrat - Mrs Odile Schiltz (E12 in the scientific report)

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	2
N7: Number of staff members with a HDR or a similar grade	3	2

- Appreciation on the results:

— Relevance and originality of the research conducted, quality and impact of the results:

Not surprisingly for a methods/technique-oriented team, the major interest of the group deals with the development and further refinement of methods/techniques by studying relevant research problems that are provided by collaborating groups. In the past period, the team has made significant progress in the development of analysis software and in the mass spectrometric analysis of low abundance proteins and made important contributions to three major research areas (proteasome, proteome analysis of endothelial cells, identification of interaction partners of THAPs) thereby directly contributing to the success of several IPBS teams.

The team has contributed to 40 original manuscripts, some of them have been published in highly reputed journals including PNAS and EMBO J, and 3 book chapters. Importantly and indicating that the team not only acts as a "service provider" for other teams, the number of first and/or senior author publications of the team has significantly increased in recent years. One thesis has been finished in the past period.

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

3 invited talks are mentioned. This team was able to attract several postdoctoral fellows and three graduate students. A significant number of grants from charities, industry, public funding bodies (mainly due to equipment). Part of several international and national programs.

This team is well connected at the national and international level. Clearly, this team is essential for IPBS.

- Appreciation on the strategy, governance and life of the team or project:

Several members of the team are involved in teaching and through the platform make significant contributions to the environment in Toulouse and Cancéropole GSO.

- Appreciation on the project:

The projects (refinement of mass spectrometry methods, development of bioinformatic tools; in particular, the last issue remains a major bottleneck in the analysis of high throughput data) are a logical continuation of the previous period with somewhat more emphasis on the analysis of posttranslational modification (a development that can be observed worldwide). In addition, the team will get involved in the discovery of prognostic and/or diagnostic biomarkers. The outcome of this endeavour is opened but the project is certainly interesting.

Similar projects are, of course, pursued in various mass spectrometry laboratories worldwide. However, this is required to find the most appropriate solutions for the various applications and, since each laboratory usually addresses similar technical questions using different model systems (depending on their scientific environment), the project should be considered as original.

- Conclusion:

— Summary:

Project "essential" for the success of IPBS.

— Strengths and opportunities:

The team is well connected to other teams of IPBS and, therefore, access to interesting projects. Different projects provide the opportunity to further develop/refine various aspects of mass spectrometry and its (bioinformatic) analysis.

— Weaknesses and threats:

The quality of the team's research depends largely on the quality of the projects of the collaborating groups. The proposed proteasome project appears to be the least attractive (this is a highly competitive area and the approach proposed is not very original).

— Recommendations:

The panel advises the team to be selective in the choice of its projects.

Name of the team : E11 – "Structural Biophysics"

Name of team leader : Mr Lionel MOUREY (E13 in the scientific report)

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1,4	1,4
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		1 *
N6: Number of Ph.D. students (Form 2.7 of the application file)	2 **	3 **
N7: Number of staff members with a HDR or a similar grade	2	4

* Karine Rattier, other engineer, non indicated in our "SV-UMR5089-JPGirard-3.5-Projetformulaire-S2-10-09-09.xls" table 2.6.

** included two thesis 50% in co-direction with :

- UMR 5068, Synthèse et Physicochimie de molécules d'intérêt biologique, SPCMIB, co-director JC Plaquevent for Romain Galy.
- UMR 5504, Laboratoire d'ingénierie des systèmes biologiques et des procédés, co-director M. Remaud-Simeon for Frederic Guerin.

The team is highly specialized in solving protein structures through X-ray crystallography, using the PICT-IBISA platform. It is involved in all the steps from production and purification of recombinant proteins up to the 3D analysis in order to characterize their structure function relationships. It is also obvious that the group addresses a wide spectrum of relevant biological and medical questions. Mycobacterial diseases are in the uprise again as many bacterial strains have developed resistance against common antibiotics. The biochemical and structural characterization by crystallography of enzymes of the bacterial metabolism is of utmost importance. The list of structures published or under investigation is extremely impressive. The group is involved in a number of international collaborations and has attracted a substantial number of grants. Within the last years, the structures of about twenty proteins have been investigated, mainly in collaboration with the Department "Molecular mechanisms of Mycobacterial infections". The team has also been involved in the characterization of new protein families and enzymes for biotechnological applications, as well as in two methodological developments. The team is thus quite active and due to the critical importance of protein structures, it plays an important role in the Institute. Since 2005, three PhD theses have been defended and 19 papers as well as two book contributions have been published. Two of these papers have been published in journals with impact factors IF > 10 (Science and Nat. Biotechnol), 7 papers have been published in journals with 5<IF< 10 (J Biol Chem x3, Nucleic Acids Res, Embo J), 8 in journals with 2<IF<5. Nevertheless, it should be mentioned that 6 out of these papers (including the Nat Biotechnol one) were published during the post-doctoral training of one team member. It should also be noted that the publication activity of some team members is rather low.

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

The staff members perform scientific evaluation in international grant agencies. However, only one invited conference is reported in the activity report. Further efforts should be done in the future to improve this last point. The team recruited a CR and attracted a regular flow of PhD students.

During the last years, the team has shown a very good ability to raise funds, with notably two european grants and two ANR grants. Two important grants have also been attributed to the PICT IBISA platform, to which the team provides a major contribution.

The team does not seem to be involved in constituted international networks, but it collaborates with European laboratories (Switzerland, Holland, Germany) and one USA laboratory. The team collaborates also with several French groups.

The team deposited 15 crystal structures in the Protein Data Bank.

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

The team strongly contributes to teaching, mainly through two professor assistants and one professor. Members of the group are responsible for teaching units or diploma and contribute to several committees.

- Appreciation on the project :

The proposed project is a logical follow-up of the actually developped one. A major part of this project is based on the continuation of the work on Mycobacteria proteins, which should provide important information for the fight against tubercolosis. Another interesting aim will be the determination of the structure of the gamma-tubulin complex protein GCP4 that plays a key role in microtubule nucleation. A new and exciting part of the project will be the implementation of fragment-based drug discovery within the PICT, in order to design new drug candidates. In respect with the forces and expertises being involved, a large part of the proposed project appears feasible. As the research is of medical relevance translational aspects should be considered and contacts with pharmaceutical companies should be established.

- Conclusion :

— Summary :

The team plays a strategical role within the IPBS and the PICT platform, through its expertise in structure protein determination. This kind of activity is of central importance for the objectives of the Institute on the characterization of fundamental biological mechanisms in order to develop pharmalogical applications. Through the PICT platform, the team has access to state-of-the-art equipment and facilities to perform the described projects.

— Strengths and opportunities :

The team is active and obtains excellent results in raising funds. The team appears as a major support for the Department “Molecular mechanisms of Mycobacterial infections”. The proposed developments in structural pharmacology are timely and promising.

— Weaknesses and threats :

Though the team is active in protein structure resolution, its productivity in terms of publications as well as its international visibility could be improved. Moreover, the involvement of the different team members to the research projects appears somewhat unbalanced.

— Recommendations :

The team is encouraged to be more ambitious in writing papers and participating in international networks and conferences.

Name of the team : E12 – "Cell Biophysics"

Name of team leader : Mrs Marie-Pierre ROLS (E14 in the scientific report – Mr Justin TEISSIE)

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	3 *
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1,5	1,5
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	1
N7: Number of staff members with a HDR or a similar grade	4	4

- Appreciation on the results:

The Cell biophysics team is highly specialized and recognized in the characterization and applications of membrane changes under electrical gradients. The main objective of the team was to investigate the molecular mechanisms underlying the changes in the membrane organization, as well as their consequences on internalization of small molecules, plasmids and siRNA. More recently, these investigations were extended on tissues, using fluorescence imaging in live animals. Finally, the team members apply their knowledge for treating tumors in horses, using cisplatin electrochimiotherapy. Through state-of-the-art fluorescence microscopy techniques, important data on the electropermeabilized organization of the membrane and the pathway followed by plasmids have been obtained. Moreover, using intravital microscopy and the dorsal window methodology, the tissue organization changes due to electropermeabilization were visualized. Close to 40 publications have been published since 2005. Two of them were published in journals with impact factors IF> 10 (Nature Chem Biol and Nano Letters), 5 of them in journals with 5<IF<10 (Biophys J, Mol Cancer therapy, Cancer Res) and 23 in journals with IF between 2 and 5. Two chapters in books have also been published and two PhD thesis have been defended. The productivity of the team is excellent, especially in the case of the PIs.

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

Three members of the team received an innovation award from the Midi-Pyrénées region. The PIs are well recognized at the international level, as shown by their numerous invitations to and organization of international conferences, mainly in Europe. Moreover, one of the PIs is in the editorial board of three international journals. The team is attractive for students, since actually three post-docs and 4 PhD students (most of them being french) are working in this team.

The team shows an impressive ability to raise funds, with current participation to two european contracts and one INCA DAAD contract with Germany. The team also participates or has participated to four ANR projects as well as to projects funded by AFM, INCA, DGA, InNaBioSanté.

The team is involved in two FP7 European networks and a large number of international collaborations with European laboratories (Slovenia and Germany, mainly). The team collaborates also with many groups in Toulouse and in the whole country.

A significant part of the research projects developed in the team has potential applications in the area of gene, siRNA and shRNA delivery, notably for cancer treatment. An interesting application has been obtained in the veterinary field, for curing horse sarcoids. It is nevertheless surprising, that no patent accompanies these applied data.

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

The team has been reorganized in 2007 on the request of the IPBS direction, by its merging with part of the former team of biotechnology of proteins. These new members stopped their former research projects, and develop now new research axes on DNA aptamers. The team and notably, its leaders are strongly active in organizing and participating in conferences, summer schools and workshops, which likely feed the emergence of new projects and collaborations. The team contributes to teaching, mainly through its two professor assistants. The PI is the president of the scientific committee of one of the doctoral schools in the Paul Sabatier University.

- Appreciation on the project :

The proposed project is divided in two main research axes. The first one is a logical continuation of the projects developed so far on the mechanism and applications of membrane permeabilization under an external electric field. The ultimate aim is to describe at a molecular level, how the electric field modifies the transport properties of membranes for a various number of molecules of therapeutic interest, such as anticancer drugs, siRNA, plasmid DNA and aptamers. These multidisciplinary studies which combine state of art techniques, notably in the fluorescence imaging field, will be performed on a large range of systems, starting from giant unilamelar vesicles up to live animals. The projects in this research axis are timely, relevant and highly promising for their potential applications in therapy. Moreover, the strong expertise of the key players provides good confidence on the success of these projects.

The second research axis is based on the development of new tools for delivery, targeting and diagnosis. For electrotransfer and imaging, the objective will be to adapt pulsed high voltage generators to optimize the DNA uptake, to design adapted pulsation chambers for direct visualization of the electrotransfer processes and to adapt the in vivo imaging tools, for monitoring the expression of fluorescent proteins that follows the electrotransfer process. Another project is based on the development of DNA aptamers for diagnosis and therapeutic purposes, notably in respect with ovarian cancers. This project shows interesting application perspectives. A last project is based on combining electrochemotherapy with electrogenetherapy (by expressing an IL12 coding plasmid) for achieving a total eradication of tumors in horses, including their metastasis.

- Conclusion :

— Summary :

The research projects of the cell Biophysics team, during the last years have been clearly focused on the molecular mechanism and applications of membrane permeabilization under external electrical fields. The project for the next four years, is in large part, a logical continuation of the on-going research.

In summary, the committee supports the project proposal without the least reservation.

— Strengths and opportunities :

The productivity, funding and participation of the team to European networks are excellent. The Cell Biophysics team is internationally recognized for its expertise in membrane permeabilization under electric fields. The multidisciplinary and multi-scale projects related to electropermeabilization are efficiently managed in an integrated way.

— Weaknesses and threats :

The panel considered that there were possibly too many questions addressed.

— Recommendations :

The panel recomends a selection in the number of biological questions to be addressed.

Name of the team : E13 – "Functional Dynamics of Biological membranes and DNA Molecules"

Name of team leader : Mrs Laurence SALOME

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0,7	0,7
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	0,5*
N7: Number of staff members with a HDR or a similar grade	2	3

- Appreciation on the results:

The team is involved in characterizing the biophysical principles that govern molecular assembly and function of membrane proteins. This protein class is of outermost interest in a biological and certainly pharmacological view. The team uses state-of-the-art fluorescence-based instrumentation and methodologies, such as single particle tracking (SPT) and Fluorescence Recovery After Photobleaching (FRAP) techniques. The team members not only professionally use these techniques, but also develop new tools, such as the variable radius FRAP methodology, an algorithm for SPT confinement analysis, functionalized supports for simultaneous observation of multiple molecules in SPT, a fluorescent cholesterol analogue and a new type of supported bilayers. These developments are innovative and relevant for providing original responses for the investigated biological questions. The approach to study the impact of protein assembly and function upon membrane properties is a particularly interesting. Such studies are likely to add to our current view on the complex interplay of membrane topology and protein structure for membrane protein function. With an average number of more than 7 publications per year the group is very productive. The data obtained by the team on the regulation of the functions of various membrane receptors are important. Two of these papers were published in journals with impact factors IF> 10 (Science x2, both of them correspond to post-doctoral works not related to IPBS), 12 of them are published in journals with 5<IF<10 (Nucleic Acids res, J Biol Chem, Biophys J, J Control Release) and 15 in journals with IF between 2 and 5. One international patent has been deposited. Five PhD thesis have been defended since 2005. The productivity of the team is very good.

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

Only two invited conferences in French symposia are reported for the team leaders. This appears surprizing in respect with the quality of the research performed in this group. Efforts should be done especially by the team leaders to be more "aggressive" and advertise their work in international conferences. The team appears quite attractive, since three new members recently joined in. During the last years, the team projects have been funded by ANR, ERANET, "CNRS prise de risque", Université Paul Sabatier and ANRS. The actual situation seems somewhat less favorable since only a rather small grant is reported for 2009. The team does not appear to be involved in international networks, but collaboration with European laboratories (GB and Spain) is reported.

The team collaborates also with several French groups. A patent has been filed on the fluorescent cholesterol analogue, but it is not reported whether this patent has been or will be licensed to a company. The on-going project on parallelization of single molecule experiments will likely be patented too.

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

The members who joined the team recently, are logically integrated in the main stream projects of the team. The expertises of the new members appear well complementary to the existing ones and used efficiently to reach new goals and address new questions.

The team contributes to teaching, mainly through its two professor assistants. Most members of the team participate to the Master "Biologie Structurale et Fonctionnelle".

- Appreciation on the project :

The proposed project is a logical and ambitious follow-up of the research currently developped. This project includes original instrumental and methodological developments (such as dual color vrFRAP, high frequency SPT, a dedicated SPT system to explore local membrane properties and nanochips for parallelized experiments on single DNA molecules) that will provide new and decisive information on the explored systems. Among the applications of these techniques, the projects based on exploring the physical principles underlying membrane microdomains and the relationship between the functions of various receptors and their environment are timely and should afford important responses, notably in the regulation of GPCR functions, the interplay between CD4 and CCR5 receptors in HIV-1 infection, the infection mechanism by Mycobacterium tuberculosis and the control of pain. Finally, single molecule experiments on DNA molecules are expected to provide new fundamental knowledge on DNA recombination and denaturation. In respect with the forces and collaborations being involved, most of these research projects appear feasible.

- Conclusion :

— Summary :

This multidisciplinary team performs interesting and innovative research on membrane characterization and regulation of membrane protein functions. This research is fed by new instruments and methodologies developed by the team. The objectives of the team are clear and the team members use their complementary expertises cooperatively. The research projects for the four next years are sound and ambitious.

— Strengths and opportunities :

The productivity of the team is very good, with most publications being published in good to very good journals. The research is multidisciplanary and innovative, adressing important biological questions. All the team members collaborate synergically, being involved in several projects in parallel.

— Weaknesses and threats :

Though the research performed in this group is of very good level, the international visibility, notably of the team leaders, appears limited. The funding level of the team for the two last years appears surprisingly modest, in respect with the activity of the team.

— Recommendations :

Team leaders are encouraged to be more ambitious in their search for funding, participation in international networks and conferences.

Name of the team : E14 – "Amyloids & Alzheimer"

Name of team leader : Mrs Marie-Lise MADDELEIN (E16 in the scientific report)

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)		1
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results:

The team has obtained very interesting results on the structural elements and infectivity of HET-s prion that had a major impact in the scientific community. However, all these results were obtained before starting the CNRS ATIP grant. Scientific papers corresponding to the research activities of this CNRS ATIP grant have not been yet published. There are some difficulties to dissociate the research project from the results already obtained since several points of the results are stated in future terms (…will be performed…). In general, it would be also suitable to improve the quality of the presentation of the report. The team reports interesting advances in the establishment of a new method to express and purified Abeta recombinant petides in S. Coli and Abeta aggregation in Podospora anserina. These methods can be useful in future studies but no articles have been yet published at the present moment. The quality of the publications before starting the CNRS ATIP grant is excellent. It is important to underline the articles in Nature (2005) and Mol Cell (2007), as well as other interesting papers in J Biol Chem (2005) and Mol Pharmacol (2007). One collaborative paper appears as submitted and a second manuscript is reported in preparation In addition, only one Master 2 student is reported during this research period (no additional PhD students).

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

No information is provided about awards and only two invited conferences (one at national level) have been reported by the team. One post-doc from the ATIP CNRS contract and one Master 2 student are included in the team. The post-doc has not still published any scientific article with the PI. The team leader has obtained a CNRS ATIP contract as well as other grants from public institutions, charities and the Marie-Curie programme of FP7. She has been therefore rather successful in raising funds from competitive programmes. The team is involved in collaborative grants ANR (3 partners), Marie-Curie IRG (2 partners) and Fondation Biosecure (7 partners). The team maintains interesting national and international collaborations, but they have not participated in any IP or STREP of the FP7. The topic of the research activities of this team, Alzheimer's disease and transmissible spongiform encephalopaties, has a great potential health and socio-economic interest. The methods that have been established by the team should be useful to provide interesting results, although no articles have been yet published with these new methods.

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

The team is involved in teaching activities in one master and reports the participation in a workshop in Toulouse.

- Appreciation on the project :

From the information, the committee is unable to judge the long-term propects of the project. The techniques that have been validated for the team to express and purify Abeta recombinant petides in E. coli and Abeta aggregation in Podospora anserina are very interesting. These methods can be very useful in future studies.

- Conclusion :

— Strengths and opportunities :

The group targets and important research area at the interface of neuro –and structural biology. There is no doubt that such research lines must be present at an internationally competitive research institution.

— Weaknesses and threats :

The panel expressed concern about the future of this group if the expectations that led to the creation of the ATIPE/CNRS team, and the hopes engendered by the technologies developed do not concretize in visible achievements and publication in a near future. Evolution of this team needs careful monitoring.

— Recommendations :

If, in the next 2-3 years, no significant scientific accomplishments are made in this highly competitive research area, the committee recommends to relocate the team or to integrate it into a more suited scientific environment.

Name of the team : E15 – "Molecular and Functional Pharmacology of Neuropeptide Receptors"

Name of team leader : Mr Jean-Marie ZAJAC (E17 in the scientific report)

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)		
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)		
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results:

The results that have been previously obtained by this team are focussed on understanding the role of the NPFF system in the nervous system. Some of these results are of high interest, in particular the identification of the first selective antagonist of NPFF receptors (collaboration with a lab in Strabourg), the identification by FRET techniques of a hetero-oligomerization of NPFF2 and mu opioid receptors and the results about the relationships between NPFF and morphine in the model of chronic cancer pain. However, the relevance of other findings is limited and the results have been published in scientific journals of medium/low impact. The quality of the publications is limited. The most relevant paper (PNAS, 2006) was obtained from a collaboration. From 2005, two additional papers are of particular relevance: J Biol Chem 2007 and Mol Pharmacol 2005. However, the other articles have been published in scientific journals of medium/low impact. Only two conferences at the national level have been reported by the team. In addition, only one thesis has been achieved in this period, which is surprising considering that three full time researchers are included in the team.

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

No information is provided about awards and only two conferences at the national level have been reported by the team. It is really surprising that only one thesis has been achieved during this four years period and that neither students nor post-docs are now included in the team. Only a modest ANR grant (93.000 euros) has been obtained in this four years period. The team does not seem involved in national or international scientific networks. The team maintains interesting national and international collaborations. The collaborations with the Queen's University and the Institut Gilbert Laustriat are of particular interest in terms of relevance of the results obtained. The topic of the research activities of this team could be of potential health and socio-economic interest in terms of elucidating new strategies to decrease opioid tolerance and to enhance opioid analgesia. However, the results that more clearly show this possible application has been obtained in collaboration with another research team.

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

The absence of students and post-docs raises questions about the organization of the team and the attractiveness of the research. The team is involved in teaching activities in three different masters.

- Appreciation on the project :

The research project will investigate multiple aspects of the structure-function, cellular and molecular mechanisms, and pharmacology of NPFF receptors. A particular effort will be devoted to the characterisation of new NPFF lgands in collaboration with several chemistry groups. The panel recommends to pay a particular attention to the development of new antagonists of these receptors since they could have a particular clinical interest. The rational for the search of bivalent NPFF2- MOP ligands is not clearly justified. The committee raises doubts about the potential impact of some of the experimental approaches, in particular the large effort that is devoted to the characterisation of the MOP/NPFF heteromers. Are these heteromers so relevant to devote such an important experimental effort? In contrast, other interesting aspects are explained in a superficial way, such as the interactions between NPFF receptors and other opioid receptors or the interactions at the neuronal level. Of particular interest seems the studies focussed on the pharmacological characterisation of the NPFF receptors. However, a more detailed explanation of this interesting topc should be provided (how will the transgenic and conditional knockout approaches be developed ? How will the proteomic strategy be used ? How will the reward and addiction studies be addressed ?).

The research project includes interesting approaches to elucidate the structure-function, cellular and neuronal mechanisms related to NPFF function. However, the use of these techniques should focus on those aspects of the NPFF functions that could have more impact.

- Conclusion :

— Summary :

The team works on understanding the role of the NPFF system in the nervous system. Some of these results are of high interest, in particular the identification of the first selective antagonist of NPFF receptors, the identification by FRET techniques of a hetero-oligomerization of NPFF2 and mu opioid receptors and the results about the relationships between NPFF and morphine in the model of chronic cancer pain.

— Strengths and opportunities :

The project has a high relevance for the pharmacological profile of the institute.

— Weaknesses and threats :

The scientific relevance of the planned investigation of the heterodimerization of the receptors has been questioned by the committee.

— Recommendations :

The panel advises the group leader to make all possible efforts to increase the visibility and demonstrate the relevance of his project. This should particularly be obtained by attracting students and post docs, and raising significant funding.

Name of the team : E16 – "Mycobacterial Envelopes : Structure Biosynthesis and Functions"

Name of team leader : Mr Mamadou DAFFE (E19 in the scientific report)

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5	6
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		1*
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	1
N7: Number of staff members with a HDR or a similar grade	5	6

- Appreciation on the results:

This unit is part of one of the premiere groups in the biochemical and structural analysis of mycobacterial cell wall components. Only Colorado State University (where the PI was trained) has a comparable collection of scientists. Some of the research appears narrow in focus but, within the institute, this is balanced by broader programs addressing basic biological questions. The PI reports 60 primary publications from this group over the 5 year period. Many of these papers are in first rate journals, testifying to the rigor of the published data. There are a reasonable number of more general reviews and several papers exploring the impact of structural alterations on the biology of the bacterium in infection models. The papers include many publications demonstrating collaboration across the different laboratories in the group. The papers do not show a phenomenally high citation rate, but the focus is specialized, and the audience limited. Other output is reasonable but the number of invited presentations is quite low. The laboratory publishes many papers in collaboration with other labs in Toulouse and with outside collaborators. Many of these collaborations are long-term interactions that provide evidence of the value of this lab to the field.

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

The research has not attracted the level of recognition or awards that would be consistent with the quality of the work. The group tends to focus on "home-grown" talent rather than recruitment of scientists from abroad, although the research is truly international with many overseas collaborators. The PI has been successful in raising funds from external bodies although the lab does not participate in many of the more influential European networks. The lab is actively engaged in international research, although we don't see it playing a leading role in the larger European TB collaborations – this may be a deliberate decision! The laboratory appears to be a good training environment with a steady output of graduated students.

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

The biochemical data are rigorous and of a high quality however the committee feels that the projects are driven by chemical question and not by biological questions. This is possibly one of the reasons that they will remain relatively narrow in focus. We do notice an increasing interaction between this team and other, more junior labs in the unit where biology has a greater emphasis. This holds promise for the future.

- Appreciation on the project :

1) Identification of enzymes essential for mycobacterial physiology and putative drug targets.
2) Identification of bacterial factors that modulate the host immune response.

The drug discovery projects are based on identified targets not on unbiased screens, which play to the strength of the lab but limits the scope of the projects. Nonetheless these are valuable studies. The other projects based on cell biology and immunology are of interest and they represent more mainstream lines of research. The only concern here is to ensure that the research plays to the established strengths of the unit.

As mentioned above some of the projects in the new labs are similar to research being pursued elsewhere. This is a strength as long as the unit ensures that they take an approach that exploits their unique skills.

- Conclusion :

— Summary :

The committee members feel that this work is of extremely high quality but would gain in value and visibility by actively searching for interfaces with other biological disciplines.

— Strengths and opportunities :

The panel stressed that the PI is an extremely rigourous, acknowledged expert in the field of mycobacterial lipid structure and synthesis. He brings a unique skill set to his department. He is also a highly collaborative investigator.

— Weaknesses and threats :

The panel noticed that the group is deliberately focused in the field of mycobacterial lipids. This tends to limit the opportunity of generating interfaces with other areas of biological research.

— Recommendations :

The panel advises the PI and his team to improve their international visibility by attending and participating in international meetings more frequently.

They should also maximize their interface with other teams within IPBS.

Still, the panel wishes to reinforce its opinion that the expertise of this team is invaluable for IPBS and needs to be sustained.

Name of the team : E17 – "Molecular Mycobacterial Pathogenesis"

Name of team leader : Mr Christophe GUILHOT (E20 in the scientific report)

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)		
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	1*
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	2
N7: Number of staff members with a HDR or a similar grade	3	3

- Appreciation on the results:

This laboratory show a concentrated effort to cross the disciplinary divides between molecular biology, biochemistry and cell biology. Recent publications, such as the one in PLoSPath 09 demonstrate the willingness of the PI to explore new avenues and address questions of broader physiological significance. The PI reports 13 publications over the review period, which is excellent productivity for an investigator establishing a new lab. The papers have consistently appeared in top rank journals. Teams 16 and 17 really play extremely well of each others' strengths to produce some high-quality papers. The PI also has some notable foreign and French collaborators.

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

The PI has had a couple of invitations to present at International meetings but fewer than the panel would have expected. The team leader is an Editorial Board Member for J. Biol. Chem. Once again, the group tends to focus on "home-grown" talent rather than recruitment of scientists from abroad, although the research is truly international with many overseas collaborators. The PI has some modest success in raising funds, predominantly as part of consortia. This is an area where one would expect greater activity in the future. This team is actively engaged in international research.The laboratory appears to be establishing an effective training environment for graduate students with one successful defense and another scheduled for this fall.

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

The laboratory has a mix of "safe" biochemical projects that are pathway driven, and some more challenging questions of biological function that probe the role of lipid/lipid interaction in modulating phagosome maturation. As mentioned the laboratory appears a good training environment that is extremely interactive.

- Appreciation on the project :

1) Identification of enzymes essential for mycobacterial physiology and putative drug targets.
2) Identification of bacterial factors that modulate the host immune response.

The drug discovery projects are based on identified targets not on unbiased screens, which play to the strength of the lab but limits the scope of the projects. Nonetheless these are valuable studies. The other projects based on cell biology and immunology are of interest but are not as original as one might ideally wish to see – excepting the DIM/lipid interactions, which is novel. As mentioned above the projects are a somewhat related to research lines being pursued elsewhere. This is not a weakness as long as the lab ensures that its approach plays to the strengths of the units involved. The future projects of teams 16 and 17 were described together so the comments are related.

- Conclusion :

— Summary :

This team develops an excellent combination of biochemical and genetic approaches to decipher the role of the cell wall in mycobacterial pathogenesis.

— Strengths and opportunities :

This team uses strong biochemical and molecular approaches to address biologically significant questions surrounding mycobacterial cell wall lipids and interaction with the host.

— Weaknesses and threats :

The PI should avoid peripheral interests. The international visibility does not yet fully match the quality of the work.

— Recommendations :

In a very competitive environment, this group should focus on its strengths. The PI should make all efforts to increase international visibility.

Name of the team : E18 – "Differentiation and Activation of Phagocytes"

Name of team leader : Mrs Isabelle MARIDONNEAU-PARINI (E21 in the scientific report)

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	3,5	1,5
N7: Number of staff members with a HDR or a similar grade	3	3

- Appreciation on the results:

The originality of the previous research is high (finding a defined kinase associated with 3-D migration of macrophages). An analysis of the PI's work in Scopus shows good citation rates (1721 cites in total, h-Factor 24), which underscores the relevance of the work and its acceptance in the field.

The PI has 66 papers in PubMed (68 in Scopus). 13 of these have been published in the reporting period since 2005 (1 review, 12 original papers). These are published in good journals with impact factors between 3 and 6. The latest paper has just very recently appeared in Blood (IF 10.4), an excellent journal. 8 of the 13 recent papers have the PI as senior author, 3 others have co-workers of the team as senior authors. Thus, themajority of the publishing activity originates from the group directly. This is an average output for the size of the group.

The group has graduated 3 students since 2005 (a fourth is ready to be graduated). Currently 4 PhD students are working in the lab. This is a good level. Also of note: former PhD students or technicians of the group have obtained permanent research positions (CNRS, 3 persons) or positions in industry (2 persons). This points to a high level of work quality in the group.

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

The PI has been invited to numerous national and international meetings and has also served as chairwoman. The same holds true for other members of the team. This suggests that this well known in their field. An award has not been mentioned. The quality of the recruited personnel is difficult to judge. Currently, one PhD student from Pakistan is working in the group. No other personnel from abroad (either Europe or world-wide) is reported.

The PI has multiple grants in both charities and national funding agencies. Currently running grants (2010 and longer) are 3 (2x Postdoc, 1 PhD). Despite these many French grants it is surprising that no European grants are reported. Here, probably a great source for further funding is not optimally exploited.

Numerous collaborations with scientists in France, Europe and world-wide are reported.

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

The lab members have taught 4 M2 level and 8 M1 level students since 2005. In addition, one member of the team teaches cell biology courses for the L1/2 and M1 levels (hours not reported), while the PI taught on Mycobacteria at the M2 level (30 hours) in 2005-2007. One member of the team served as member of the administrative board of the UPS as well as on the commission of experts n°65, UPS. The PI served as scientific adviser for the Ministry of Research and for AERES and she is member of the scientific council of UPS. She was also member of the scientific council n°1 of the ANRS.

- Appreciation on the project :

Molecular mechanisms of ameboid/mesenchymal migration: principally an interesting project. The approaches appeared unclear from the description but seem to have evolved much farer as deduced from, the oral presentation. This is the "backbone" of this team's project and as such appears very encouraging for the future of the team. Other encouraging lines of research have been presented that raised some remarks from the panel that are listed below. Still, overall the project has a number of very innovative and interesting aspects that deserve following up.

Phagocyte migration in context: An interesting project investigating mycobacterial infection in hck-deficient mice, which, according to previous data of the group should suffer from a macrophage-specific migration defect. In an atherosclerosis model the work seems a bit confusing (first start on a hck/fgr double mutant (whereby fgr is not explained at all)), then finding, that the hck mutant is equal to the double mutant thus proposing to work on the hck mutant alone. One asks, what should be done here, because, as described, all the work should already have been completed on the double mutant (paper will soon be written…). Finally, also a human Rheumatoid arthritis study is being planned. It is questionable, whether cells isolated from inflamed joints will maintain a changed migration behaviour, or whether this is all lost after isolation from the inflamed environment.

Podosomes in 2-D or 3-D: Investigating the dynamics of actin and hck in macrophages migrating in 3-D is an interesting approach. It is, however, questionable, whether a comparison of podosome structures made in 2-D with such structures made in 3-D is of much meaning and will yield valuable information, as the environments differ fundamentally.

Lysosome traffic: This project is not well described and structured. Key elements are not defined (e.g. frustrated phagosomes, acceptor membrane, frustrated phagocytosis assay, synchronized phagosomes), the analysis of defined lysosome-associated proteins is not described rationally but rather based on the fact, that the relevant tools are available in the lab. Further down, something is proposed to be done with "constitutively active, dominant negative constructs or siRNA", but it is not described, what.

- Conclusion :

— Summary :

The group has lifted an original project to the level of maturity. It is well funded, has an interesting research portfolio and is gaining international recognition. The project would benefit from local collaborations.

— Strengths and opportunities :

The project shows a high degree of originality in a cell type that is technically challenging. The strength is clearly the work on HCK and its immediate impact on the in vivo system as very recently demonstrated in a paper in Blood. This should be further exploited and detailed molecularly. Also the current funding seems to be solid.

— Weaknesses and threats :

The project suffers from a degree of isolation both in the institute and internationally (e.g. no EU funding).

— Recommendations :

The research portfolio as described for the coming period should be optimized according to the mentioned suggestions and European funding should be actively raised. If the PI wishes to enhance investment in the project, it would benefit the group to better integrate the research with the other programs in the institute.

Name of the team : E19 – "Mycobacterial Interactions with Host Cells"

Name of team leader : Mr Oliver NEYROLLES (E22 in the scientific report)

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	3 *	2
N7: Number of staff members with a HDR or a similar grade	1	2

* included Chuan Wang, chinese Ph.D. student, present in laboratory for a training period from october 2008 to september 2009.

- Appreciation on the results:

The originality of the previous research is high (identification of mycobacterial receptors in mice, identification of mycobacerial virulence factors for phagosmoe maturation by a novel high throughput microscopic screen), which is reflected by the reception of the work from the field. An analysis of ONs work in Scopus shows excellent citation rates (1080 cites in total, h-Factor 20), which underscores the high relevance of the work and its acceptance in the field. The Top-Paper has been cited 220 times since 2003, which is a very high rate.

The head of the research unit has 46 papers in PubMed (47 in Scopus). 11 of these have been published since 2007 (2 reviews, 9 original papers), despite the fact, that the group moved to Toulouse from Pasteur in 2007. The papers are published in good and several excellent journals (J Exp Med, PLoS Med). The latest paper has just very recently appeared in JEM (IF 15.5), a top journal. Of 24 papers published since 2005 (beginning of the report period for IPBS) 10 show the PI as first or senior author, This demonstrates that the group leader is an independent and productive scientist.

The group has graduated one student since 2006 (still at Pasteur). Currently 3 PhD students and one MSc student are working in the lab. This is a good level.

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

The PI has received the Medaille de Bronze du CNRS 2009. He has been invited to speak at numerous national and international meetings. This suggests that the PI is well known in his field. He is frequent reviewer of international journals including top journals such as Lancet and PNAS as well as for UK grant agencies. He is also full member of the editorial board of PLoS Med. He is coordinator of an ANR-funded TB project with 4 partners. Thus he has excellent communication skills and his expertise is frequently requested.

The has multiple grants in national charities and public institutions as well as the European FP6 and FP7. Currently running grants (2010 and longer) are 4 (2x French public and 2 EU) summing up to more than 900.000 € funding for the next 3 years, which is very high.

Although not specifically mentioned, European research grants typically consist of international consortia. ON also has numerous collborations with leaders in the field from France, Europe and world-wide. All this serves to demonstrate, that ON is well linked to his field and has excellent networking capabilities.

- Appreciation on the project :

C-Type lectins and mycobacterial recognition: a very interesting project. The precise signalling of human DC-SIGN shall be analyzed in primary human macrophages and bone narrow-derived dendritic cells. It shall be investigated, which signalling components (intracellular kinases, PRRs) are important to shape the response of cells towards stimulation with live bacteria or their breakdown products. Also the secretion response of T cells restimulated with DC stimulated /modulated with mycobacteria or their breakdown products shall be investigated. Finally, samples from healthy donors or TB patients (peripheral blood or BAL (from patients only)) shall be analyzed for their expression level of DC-SIGN as well as the production of Chemo-/Cytokines upon mycobacterial stimulation. The power of the approach is the significant question as well as the fact, that primary human cells shall be investigated (using siRNA), rather than cell lines.

Heavy meral fluxes and mycobacterial parasitism: A very interesting study based on a wealth of convincing previous data. Investigating the role of heavy-metal influxes (especially Zinc) into phagosomes as a method of phagocytes to restrict growth of mycobacteria, is a not very intensively studied field and shall be investigated here with a number of innovative approaches. Here, the mycobacterium itself, its intracellular survival as well as the response of the phagocyte (host cell mechanism of Zinc mobilization, involved cell transporters) shall be studied. Also the effect of this on the infection process *in vivo* will be tested (with deletion mutants) and also the levels of Zinc in human patients before and after treatment will be tested. Ultimately, the results might lead to novel treatment options.

Generally, very well written and a very exciting research concept based on a thorough knowhow.

Both new subprojects are very innovative and interesting. They nicely complement ongoing projects of the group.

- Conclusion :

— Summary :

The group is scientifically highly productive. It is extremely well funded, has a very interesting research portfolio and is highly recognized in the scientific field on the level of citations as well as invitations to conferences.

— Strengths and opportunities :

The PI brings a strong background of cellular microbiology to the institute. His expertise in pattern recognition receptors of the immune system is currently unique within the institute. The quality of the work is reflected by the very robust national and european funding.

— Weaknesses and threats :

Currently the PI has a broad portfolio of preliminary projects which at some point need to be carefully evaluated and prioritized.

— Recommendations :

The group should be fully supported.

Name of the team : E20 – "Immunochemistry and Mycobacterial Glycoconjugates"

Name of team leaders : Mr Germain PUZO – Mrs Martine GILLERON – Mr Jérôme NIGOU (E23 in the scientific report)

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	6	6
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	3	
N6: Number of Ph.D. students (Form 2.7 of the application file)	4 *	
N7: Number of staff members with a HDR or a similar grade	6	6

* included Shyam Krishna, indian Ph.D. student, present in laboratory for a training period from may 2008 to january 2010.

NB : Gérald Larrouy-Maumus, postdoctoral fellow, Merieux-Alliance support, will work in the team from 01/07/09 until 31/12/10.

- Appreciation on the results:

The PI has leveraged his expertise in the structure and biochemistry of glycolipids into exploration of immunology and the recognition of Mtb glycolipids by receptors of the innate and acquired immune system. His projects are grounded more and more in biological questions involved in processing of antigens loaded into CD1 molecules and in the interaction between lipid ligands and host PRR.

The PI reports 31 publications over the review period, which is excellent productivity for an investigator who might be regarded as the closing stages of his career. The papers are in a broad range of disciplines and in excellent journals.

The impressive aspect of the publication record over the past five years is not the number of outside collaborators but the role that more experienced researchers in this team appear to be playing. Many of the papers have staff scientist others that the PI as senior authors. This implies that the PI has been working hard to develop their independence, which bodes well for the future health of the group.

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

The PI has had several invitations to speak at international meetings and has an established reputation in the field. Once again, the group tends to focus on "home-grown" talent rather than recruitment of scientists from abroad, although the research is truly international with many overseas collaborators. The PI has competed effectively for outside support including a grant from the NIH. The lab is actively engaged in international research.

The laboratory has graduated 5 PhD students over the past 5 years and the PI as well as the other senior group members appear to be actively engaged in teaching structural and biochemical courses within the university.

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

The laboratory has undergone somewhat of a metamorphosis from straight structural and biochemical projects to projects more firmly grounded in biological questions. These questions have broader appeal and address some basic cellular processes, these look an excellent set of projects for the future.

As mentioned the laboratory appears a good training environment that is extremely interactive, and the senior faculty all participate in teaching within the University.

- Appreciation on the project:

1) Lipid Antigens and unconventional T cells.
2) Molecular basis of Innate Immune response to Mycobacterium.

Both Axes are based on an excellent foundation of preliminary data and publications and address basic questions of cellular processing machinery, innate and immune recognition of Mycobacterium, and the bacterial synthesis of these innate and immune ligands. This is an excellent range of projects.

The retirement of the PI represents a serious loss of expertise, which could place the group in a vulnerable position. Adequate resources need to be allocated to support the appropriate successor.

In of themselves the projects are being pursued elsewhere but members of the committee believe that Toulouse is almost unique with respect to the expertise available to pursue these particular questions from structure and biochemistry, through to function and biology. These projects really play to the strengths of the institute.

- Conclusion :

— Summary :

The group has done an extraordinary transition building on their expertise in biochemistry and structural biology to address problems of fundamental biological significance. Future developments should be carefully managed.

— Strengths and opportunities :

The group has applied his expertise in lipid chemistry to focus on the interaction of bacterial ligands and host receptors. The work of remodelling lipid ligand to fit into CD1 molecules is truly groundbreaking. The pattern recognition research holds similar promise.

— Weaknesses and threats :

The impeding retirement of the group leader places this group in an uncertain situation.

— Recommendations :

This group is doing outstanding research and the transition to new leadership should be monitored carefully. The new leader needs to ensure that the profile of the research is promoted as aggressively as possible.

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

Team 1: MICROENVIRONMENT, CANCER AND ADIPOCYTES

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	non noté	A

Team 2: HIGH ENDOTHELIAL VENULES (HEVs), INFLAMATION AND CANCER

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A+	A	non noté	A+

Team 3: SPHINGOSINE 1-PHOSPHATE AS A THERAPEUTIC TARGET IN CANCER

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	non noté	A

Team 4: TARGETING OF PROTEINS TO PROTEASOME IN CELL DIFFERENTIATION

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	non noté	A

Team 5: GENOTOXICOLOGY

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	B	non noté	A

Team 6: RADIOBIOLOGY AND DNA REPAIR

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	B	non noté	A+

Team 7: GENETIC INSTABILITY AND TRANSCRIPTION REGULATION

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	non noté	A

Team 8: TRANSCRIPTION AND DNA REPAIR

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	non noté	A+	non noté	A+

Team 9: NMR AND PROTEIN – MEMBRANE INTERACTIONS

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	non noté	A

Team 10: PROTEOMICS AND MASS SPECTROMETRY OF BIOMOLECULES

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	non noté	A

Team 11: STRUCTURAL BIOPHYSICS

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	non noté	A

Team 12: CELL BIOPHYSICS

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	non noté	A

Team 13: FUNCTIONAL DYNAMICS OF BIOLOGICAL MEMBRANES AND DNA MOLECULES

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	non noté	A

Team 14: AMYLOIDS & ALZHEIMER

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
C	non noté	C	non noté	B

Team 15: MOLECULAR AND FUNCTIONAL PHARMACOLOGY OF NEUROPEPTIDE RECEPTORS

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	A	B	non noté	B

Team 16: MYCOBACTERIAL ENVELOPES: STRUCTURE BIOSYNTHESIS AND FUNCTIONS

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	non noté	A

Team 17: MOLECULAR MYCOBACTERIAL PATHOGENESIS

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	non noté	A

Team 18: DIFFERENTIATION AND ACTIVATION OF PHAGOCYTES

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	non noté	A

Team 19: MYCOBACTERIAL INTERACTIONS WITH HOST CELLS

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A+	A+	non noté	A+

Team 20: IMMUNOCHEMISTRY AND MYCOBACTERIAL GLYCOCONJUGATES

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A+	A	non noté	A

Direction de la Recherche

Toulouse, le 08 Mars 2010

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Le Président

au

Président du comité d'experts de l'AERES

Objet : Observations de portée générale sur le rapport d'évaluation
de l'unité **«Institut de Pharmacologie et de Biologie Structurale » - UMR 5089**
portée par **Jean-Philippe Girard**

Monsieur le Président,

Je vous remercie pour l'évaluation de l'Institut de Pharmacologie et de Biologie Structurale (IPBS-UMR 5089) dirigé par Jean-Philippe Girard et rattaché à mon établissement.

Je me réjouis que le Comité d'Experts de l'AERES ait reconnu la grande qualité des recherches menées à l'IPBS et le rôle clé que joue cet Institut au sein de l'Université. Les points à améliorer seront discutés avec le Directeur d'Unité dans un esprit constructif pour l'avenir de la recherche à l'Université.

Vous trouverez ci-dessous un message du Directeur d'Unité apportant quelques observations sur le Rapport d'Evaluation de l'AERES.

Je vous prie de croire, Monsieur le Président, à l'expression de ma meilleure considération.

Le Président de l'Université

Gilles FOURTANIER

Institut de Pharmacologie et de Biologie Structurale – UMR5089

Comments on the report from the AERES review committee

A/ Comments on the overall appreciation of the research unit

We are grateful to the AERES Committee for its positive comments and constructive recommendations. All members of the Institute appreciated the exchanges with the experts during the three days. We are happy that the Committee stressed "the global scientific quality and ambition of IPBS and the fact that IPBS stands as an original and essential structure in the French scientific community that appears irreplaceable in its basic approach of pharmacology and capacity to lay proper conditions for the development of novel therapeutic approaches in cancer and infection".

We agree with the Committee that the strengths of IPBS reside in the quality of its scientific staff, its state-of-the-art technological facilities, its strong links with Université Paul Sabatier and its capacity to develop cutting edge basic research in original topics of medical relevance (cancer, tuberculosis).

We also agree that we need to increase our international visibility and we thank the Committee for suggesting several tools/actions that will help us to significantly increase the visibility of IPBS outside. We would like to ensure the Committee that these actions will be a top priority in the coming months/years. This will include (but will not be limited to) an increase in the number of "IPBS Prestige Days Conferences" where renowned international leaders are invited to share their views with local IPBS speakers, an increase in the participation of IPBS scientists to important international meetings (fellowships for IPBS PhD students and post-docs) and the release of a new attractive (english) Web site.

As suggested by the Committee, we will also make efforts to increase the interactions between the teams of the three departments. We are confident the recent reorganization of IPBS departments, the scientific animation going on (inter-department meetings such as the Infection, Immunity and Immunology Club) and internal calls (such as the recent IPBS Structural Biology Call) will rapidly result in a significant increase in the number of multi-disciplinary projects at the interface of disciplines.

Finally, we acknowledge that we have a clear defect in technical support, particularly for some of the teams and facilities (animal facility, …), and we will work with Université Paul Sabatier and CNRS to rapidly ameliorate this situation.

In conclusion, we would like to thank again the Committee for its hard work (55 pages report !) and recommendations that will be very helpful for the future of IPBS.

B/ Comments on the specific appreciation team by team

The PIs of IPBS teams thank the members of the Committee for their comments and constructive remarks. Although they generally agree with these remarks, some of the PIs would like to provide some comments and, in some cases, additional information. Since the remarks of the AERES committee will be publicly available, we think the team leaders should be given an opportunity to express their views.

E2 - High endothelial venules (HEVs), Inflammation and Cancer - Jean Philippe Girard

We thank the Committee for the generous comments and recommendations. We agree that we need to further increase the international visibility of the team. However, we would like to point out that the team has already a rather good visibility for its work on HEV (with > 300 citations, the landmark review we published on HEV is the most cited review on the topic). The team is recognized as the leading team in Europe on HEV, and because of its recognized expertise, became a member of the European Network of Excellence MAIN "Migration and Inflammation" (the only French team in this Network). Members of the team (PI and PhD students) gave 7 talks at MAIN's international meetings during the last period. They also presented their results on HEV topic in international meetings in Japan (Kobe) and USA (Gordon Research Conference).

In addition, our work on the two novel human proteins that we discovered in 2003, THAP1 and IL-33 (7 publications in very good journals, including PNAS 2005, Blood 2007, PNAS 2007, J Biol Chem 2008, EMBO R 2008, PNAS 2009, J Biol Chem 2010; team members are in 1st and last author positions in all these publications), has recently attracted a lot of international attention. Mutations in THAP1 have been found to cause DYT6 primary torsion dystonia, a human neurological disease characterized by abnormal muscle contractions (Nature Genetics 2009), and IL-33 is now recognized as a major IL-1-like tissue-derived cytokine. Our 2007 PNAS paper on IL-33 already got > 100 citations and our 5 publications on IL-33 are highlighted in review articles recently published in Immunity and Nature Reviews Immunology. In addition, the PI of the team was a Distinguished Speaker on IL-33 at the recent GTCBio "Cytokine and Inflammation International Conference" in San Diego, California (January 28-29th, 2010).

Finally, it is important to mention that during the past few years, the PI reviewed > 10 manuscripts on IL-33 and served as a referee for several high impact journals such as Nature Rev Immunol, J Exp Med and Blood (on both IL-33 and HEV topics). The PI was also invited to write a chapter on HEV in Endothelial Biomedicine, the prestigious Encyclopaedia of the Endothelium (1856 pages, edited by W Aird, Harvard Medical School).

For all these reasons, we are confident the international visibility of the team will significantly increase in the coming years.

E4 - Targeting of proteins to proteasome in cell differentiation - Pierre Lutz and Christel Moog-Lutz

Regarding the scientific production of our team, we would like to mention that the group leaders are the senior authors of most of their articles that were published in high impact journals (2 Journal of Biological Chemistry in 2005, Blood 2008, Cell Death & Differentiation 2009, Molecular & Cellular Proteomics 2009) during the reporting period.
We would also like to mention that two thesis have been defended in the reporting period.

In response to the "weaknesses and threats" mentioned by the AERES committee, we would like to indicate the following informations:

- The label-free quantitative proteomic strategy has been successfully used to demonstrate the loss of all ASB2 substrates identified so far. These results have been published in two scientific articles (Molecular & Cellular Proteomics and PloS One in 2009).
- The large scale *in vitro* project approach will be carried out on a collaborative basis with two other groups with internationally recognized expertise in ubiquitylation (M. Piechaczyk, IGMM-CNRS, UMR 5535, Montpellier and O. Coux, CRBM-CNRS UMR 5237, Montpellier).

E6 - Radiobiology and DNA repair - Patrick Calsou

Regarding the chapter "Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners", the team would like to remind the information present in the "scientific report 2005-2009":

11 invited talks at international meetings are mentioned as well as 20 seminars in France or abroad.
The team proposed and organized the 1rst German-French International Meeting in « DNA repair, Damage signaling and Carcinogenesis » in 2007 (the 2nd was in Konstanz, 2009 and the 3rd will be in Strasbourg, 2011) as well as 5 national workshops.
The team is one over the 100 "équipes labellisées" in France by the "LIGUE Nationale contre le Cancer".

E7 - Instabilité Génétique et Régulation Transcriptionnelle - Amine Khamlichi

The following remarks are mainly intended to clarify some of the points raised by the committee in his constructive recommendations.

1- Internal collaborations within IPBS.
We are already engaged in a collaborative work with Lionel Mourey's team in Structural biology department. And we will very shortly start a proteomics project that will be performed in collaboration with Bernard Monsarrat on AID cofactors. Unfortunately, space (report) and time (talk) limitations did not allow us to describe their content in any detail.

2- Diversification of the experimental approaches.
While focusing more on the main results and the questions we are asking for the future, we didn't mention in detail the experimental settings. This may have given the impression that our main theme is mouse genetics. We are actually using and planning to use various approaches including biochemical (chromatin analysis, protein analysis,…), structural biology and proteomics (see above), confocal microscopy and immunohistochemistry, depending on the question being asked.

3- International visibility and international grants:
The recommendation is well taken. We will do our best, we hope that our collaborations with leading groups (FW Alt, MS Neuberger, MR Lieber, PJ Gearhart,…) will increase our international visibility and might help raising international funds.

E11 - Structural Biophysics - Lionel Mourey

The team appreciates and will take into account the comments of the review committee, especially with respect to international visibility and publication throughput. Concerning the latter point, several results pertaining to new and/or risky projects of the team are in the process of publication.

The sentence "Moreover, the involvement of the different team members to the research projects appears somewhat unbalanced" might be interpreted in several ways. We want to assert that every member of the team is deeply involved in his/her project/s and we do feel that the distribution of FTEs is well balanced and in any case reflects the current needs of the projects.

E13 - Dynamics of biological membranes and DNA molecules - Laurence Salomé

After editing the documents for the AERES, the team leader has already succeeded in obtaining new funding:

- 260 k€ from ANR PIRIBio (2010-2012) for the collaborative project GPCR D-I-F "Regulation of GPCR function by heteromerization and dynamic organization of receptors in the membrane"
- 70 k€ from AVAMIP (2010) for the parallelized experiments on single DNA molecules.

In addition, Nikon France supports the development of the dual color vrFRAP through lending of equipment.

E14 - Amyloids & Alzheimer - Marie-Lise Maddelein

The team « Amyloids & Alzheimer » (ATIP convention established the 15th December 2007) would like to provide additional information regarding publications. The team leader is author of 5 publications since her arrival at IPBS in 2007 (*Mol. Cell, J. Mol. Biol., Prion, ChemBioChem, Mol. Pharmacol*.) and 2 book chapters. The post-doctoral researcher, L. Perrone (member of the team from June 2008 to May 2009) as well as the Master II student, A. Mockel are authors in the publication issued from a collaborative work:

- **Perrone L**, Mothes E, Vignes M, **Mockel A**, Figueroa C, Miquel MC, **Maddelein ML,** Faller P. *Copper transfer from Cu-Abeta to human serum albumin inhibits aggregation, radical production and reduces Abeta toxicity*. ***Chembiochem.*** 2010;11(1):110-8. Online 10 November 2009.

Thanks to the AERES Committee to consider the great potential of the research subject. As indicated by the Committee, the methods performed by the team to study Abeta aggregation are very useful. The team is confident about significant scientific accomplishments in a near future (one manuscript about the production of recombinant Abeta, and one manuscript about the effect of familial AD mutations on *in vivo* Abeta aggregation should be accepted in 2010).

E15 - Molecular and Functional Pharmacology of Neuropeptide Receptors - Jean Marie Zajac

The scientific relevance of the study of heterodimerization of the NPFF and opioid receptors has already been evaluated and financed by ANR PIRIbio 445026 : 36 months fundings 595 590 €. The team is project manager and this program involves three national collaborations.
One doctoral student and one engineer (CDD ANR) should be added in the composition of the team. The low number of thesis is due to the fact that half of the team has been renewed recently.

E16- Mycobacterial Envelopes : Structure Biosynthesis and Functions - Mamadou Daffe

We have to thank the panel for its hard work on a so multi-disciplinary institute and are indeed pleased to read that "*the committee members feel that the work (of my group) is of extremely high quality…*" and "*the expertise of this team is invaluable for IPBS and needs to be sustained.* However, the panel also points out that "(the work) would gain in value and visibility by actively searching for interfaces with other biological disciplines".; We will make all efforts to take into account the suggestions of the panel in the forthcoming period.
Nevertheless, this conclusion also raises two remarks from our side:

(i) as a possible reason of the "limited interfaces with other areas of biological research" the panel has noticed the deliberate focus on mycobacterial lipids of the group; on the other hand, the

committee members have reported as a positive point in “The appreciation on the results” of team 17 that “teams 16 and 17 really play extremely well each other’s strengths to produce some high-quality papers”. In addition, one of the strengths of the department “Molecular Mechanisms of Mycobacterial Infections” (3MI) is the complementary expertises of the teams that composed it, which covered the structural analysis, enzymology, genetics, cell biology and molecular microbiology. This is an important point for my group to deliberately collaborate with other teams of the department 3MI and of the IPBS; these collaborations have produced during the last 4 years 17 original papers (and two reviews) published with workers from 4 out of the 5 teams that compose the department, which underlines the central role of our unit due to the key role of the biogenesis of the tubercle bacillus envelope in the mechanisms of pathogenicity. These include “*biological questions*” in determining the impact of inactivating genes encoding proteins involved in the synthesis of mycolic acids and glucan, two chemically-defined molecules in the team, on the virulence of the resulting tubercle bacillus in macrophages and mice, and on the formation of granulomes. Furthermore, my group has “*generated interfaces with other areas of biological sciences*” by using new physical concepts in electron microscopy and succeeded to show, for the first time, the existence of a true outer membrane in Gram-positive mycobacteria and, accordingly, to propose a new working model that fits with all the current data. To “*maximize their interface with other teams within IPBS*” we have also collaborated with the NMR and Proteomics platforms and the PI coordinates a Région Midi-Pyrénées-funded project on Mycobacteria & Cancer, MYCA, which involved Sanofi-Aventis and teams from the 3 departments of IPBS. Likewise, in the drug design approach we collaborated with IPBS colleagues to solve the 3D structures of the target and inhibitors.

(ii) in terms of international visibility of “*focused*” work, it has to be noticed that more than 1/3 (23/60) of the published work was performed primarily with overseas collaborators, which was noted by the panel in “Strengths and opportunities”. In addition, the PI is an Associate Editor of a well-known journal, *Microbiology*, has declined the invitation to be part of that of *J. Biol. Chem.*, to avoid cumulating the editing work, and was a member of the advisory board of *Mol. Microbiol.* Furthermore, the PI is regularly reviewing papers from well-impacted Journals, such as Science and PNAS, and grant applications from abroad (UK, Austria, France). He has also been selected by the American Society for Microbiology to edit the reference book on the Mycobacterial envelope (2008). The PI has been invited as a speaker in international symposia such as the Keystone symposium.

Finally, we would like to insist on two strengths of our group, passed unnoticed in the report:

(i) the collaboration with the big pharmaceutical industry, which generated both funds and one licence, and the number of both priority patents (4) and extensions (4), a deliberate strategy to reach one of the goals of IPBS;

(ii) the particularly great contribution of the 5 associate professors, who represent half of the permanent staff of the group, to the teaching, training managing of Masters and related duties at the University, in parallel to their bench work.

E17- Molecular Mycobacterial Pathogenesis - Christophe Guilhot

The team leader would like to thank the expert panel for his thorough analysis of the organisation and work perfomed at the IPBS and for the conclusion that team E17 “develops an excellent combination of biochemical and genetic approaches to decipher the role of the cell wall in mycobacterial pathogenesis”. However, the expert panel expressed concerns regarding the fund raising activity and the international visibility of the team leader. On these two points, the PI would like to provide precision. Concerning the funding, seven grants (corresponding to 465 keuros) were obtained by his team during the last quadrennial period, with four of them coordinated by the PI. For the next quadrennial period, the team leader has obtained in 2009 four new grants (corresponding to 645 keuros for the team E17) from National and European sources. The main

grant (label “Equipe FRM” 2009, 300 keuros) was awarded to the PI acknowledging the originality and excellence of the research programs of his team (Ref. Press release from the FRM). Therefore, the team has already secured most of the funding required to realise the various proposed projects and the PI will continue to be actively engaged in the fund raising activity. Regarding the international visibility, this point may certainly be improved. However, the team leader would like to point out that he was invited as speaker to several major international meetings on tuberculosis (Keystone and Stockholm meetings in 2005) and on Molecular Microbiology (EMBO conference 2006) and that he will chair a session at the Annual Meeting of the American Society of Microbiology in 2010. He has also been solicited to contribute to 3 book chapters in the last four years and has been invited to join the J. Biol. Chem. Editorial Board in 2008.

E-18 - Differentiation and activation of phagocytes - Isabelle Maridonneau-Parini

The AERES committee has considered that our main research project on phagocyte migration and Hck is innovative, interesting, technically challenging, mature and relevant. Other encouraging lines of research have been presented that raised some remarks.
Remarks first concern collaborations with groups that are specialized in pathologies characterized by deleterious tissue infiltration of macrophages including atherosclerosis and rheumatoid arthritis. In 2007, at the beginning of our collaboration on the atherosclerosis project, phagocyte migration defects had been described in double Hck/Fgr knock-out only. This is why we used these mice instead of single Hck knock-out mice and this was argued in the report. Now, from our results published in Blood 2010, we know that Hck is a main actor of phagocyte 3D migration, which prompts us to look at atherosclerosis in Hck-/- mice. Regarding rheumatoid arthritis, we agree with the committee that the risk associated with the project makes it a low-priority project.
Few remarks were related to projects that are specific to the group. In the study of podosomes in 3D, the comparison with 2D is mandatory since up to now, podosomal structures have only been studied in 2D and therefore are the only reference to link our results to. Regarding lysosomes, our group had shown that they are involved in Hck-induced podosome biogenesis. Our project to study their traffic is critical to understand the proteolytic activity of podosomes, a particularity of these structures that is directly linked to the ability of macrophages to migrate in 3D. To carry out this project, we will benefit from the “relevant tools [now] available in the lab”.

E20- Immunochemistry and mycobacterial Glycoconjugates - Germain Puzo & Jérome Nigou

Regarding the future, we first want to stress that the team is composed of several senior scientists who are already involved in project conception, management and scientific production.

In addition, the present PI of the team "Immunochemistry and Mycobacterial Glycoconjugates", the Directors of the Department "Molecular Mechanisms of Mycobacterial Infections" and the IPBS Director are all confident that Jérôme Nigou has developed all the skills to be an excellent leader for the team in the future:
(i) he is a young talented researcher who has developed expertises in both lipid biochemistry and immunology; he is the corresponding author of many papers;
(ii) he has already managed PhD students and plays a central role in the scientific activity of the team;
(iii) he has successfully applied to grants and gained some international visibility as indicated by 3 invitations as speaker in international conferences during the last four years;

(iv) he plays a key role in the scientific animation committee of the MMMI department, he is an active member of several local committees and he is an elected member of the National Committee of CNRS (section 16).

Altogether, we think that these reasons predict well for the future health of the team.

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