Institut de biologie et chimie des protéines

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Institut de Biologie et de Chimie des Protéines

From the

University Lyon 1

CNRS

May 2010

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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 Biologie et Chimie des protéines

Requested label: UMR CNRS

N° in the case of renewal: 5086

Name of the director: M. Gilbert DELEAGE

Members of the review committee

Committee chairman

M. Lionel LARUE (Institut Curie, Orsay, France)

Other committee members

M. Christoph MULLER (EMBL, Heidelberg, Germany)

M. Niels BEHRENDT (Rigshospitalet, Copenhagen, Denmark)

M. Beat KELLER (University of Zurich, Switzerland)

M. Reinhart FASSLER (Max Planck Institute of Biochemistry, Martinsried, Germany)

Mrs. Marie-Christine RIO (IGBMC, Strasbourg, France)

M. Patrick TRIEU-CUOT (Institut Pasteur, Paris, France)

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

M. Jean-Claude MICHALSKI , CoNRS member

M. Guy BRANLANT, CNU member

Observers

AERES scientific advisor

Mrs Catherine DARGEMONT

University, School and Research Organization representatives

M. Thierry MEINNEL, CNRS

Mrs. Florence NOBLE, CNRS

M. Jean-François MORNEX, University Lyon 1

1 • Introduction

- **Date and execution of the visit**

The evaluation committee visited UMR5086 CNRS on February 1-3, 2010, from 9:00 to 19:00 on days 1 and 2 and from 9:00 to 12:00 on day 3. The visit started with a general presentation of IBCP by the Director of the centre. Each team presented their main results and perspectives for 20 min followed by a discussion of 20 min (about 10 min with the entire team and 10 min with the team leader(s)) on days 1 and 2. Members of the committee met with the different categories of personnel of the centre. Before having a meeting with representatives of CNRS, University and ITMO and with the Director of the centre. Finally, members of the evaluation committee had debriefing periods and a door-closed meeting.

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

This centre exists since 1990. The actual director is leading the institute since 2007. This centre is located within Gerland technopole in Lyon and is surrounded by other scientific centres. Currently, there are 14 teams belonging to 3 scientific departments: "Biostructures Moléculaires", "Membranes, Signalisation et Transport" and "Biologie de la Matrice et Ingénierie tissulaire". Moreover, there are three protein platforms: microanalysis, production and crystallography. A reorganization of this centre will occur in 2011 based two main themes, which are focused on two aspects "Molecular bases of infectious diseases" and "Cell and tissue dynamics", which will include twelve teams.

- **Management team**

At the administrative level, a general secretary helps the director. They are both directly in charge of the general services including accounting (6 persons), hygiene and safety (6 persons: Acmo, radioactivity, chemical and biological risks, P3, fire), valorisation (1 person), continuation education (1 person), seminar (1 person), dish cleaning (1 person). In this respect, it appears that the main functions to run an Institute are filled.

The main scientific decisions are taken in consensus with the group leaders.

- **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)	25	24
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	32	27
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	25	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	26	26
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	13	5
N6: Number of Ph.D. students (Form 2.7 of the application file)	43	21
N7: Number of staff members with a HDR or a similar grade	39	31

2 • Overall appreciation on the research unit

- **Summary**

The general goal of IBCP is to further the understanding of the function of various proteins from the molecular structure to the in vivo function using cell lines and potentially have information from tissues. It is a pluridisciplinary centre with about 170 persons. In order to achieve such goal, they established well-suited approaches from in silico, in vitro, in cellulo to in vivo. Moreover, one of their goals is to generate bioactive molecules in order to treat a very broad spectrum of human diseases such as cancer, nosocomial or viral infections, diabetes, degenerative disease and injury.

- **Strenghts and opportunities**

Pluridisciplinarity with a strong expertise in biochemistry including structural biology has been greatly appreciated. The committee believes that the new overall organization is appropriate for this pluridisciplinary centre. This centre fits nicely with the priorities of University Lyon I. As a general matter, the centre is able to efficiently raise a large amount of funding at the regional, national (ANR) and european levels for several years. The committee appreciated and supports the head of the institute to reorganize the institute and foster the interactions between groups. Stimulation grants for internal collaboration were greatly appreciated.

- **Weaknesses and threats**

In some cases, the evaluation committee had difficulties to evaluate merged groups because of the great discrepancy in the project and performances of the merged grouped. Teams co-leaderships were frequent but rarely justified and required. Visibility of the institute can be improved. Absence of announced open position led to too significant inbreeding. The committee was surprised by the existence of negative competition between teams in a pluri-disciplinary centre with a limited critical mass. The number of publications produced by the centre is fine but the quality must be improved.

- **Recommendations to the head of the research unit**

The committee recommends (i) to enhance internal interactions, (ii) to promote the recruitment of foreign young PhD students and post-doc scientists, (ii) to organize theses tutorial committees, (iii) to have weekly institute seminars (they could take advantage of the extension of the Institute to build a seminar room that can welcome 150-200 persons), students should have the opportunity to invite a certain number of external seminar speakers during each years, (iv) to favour quality instead of quantity in their publication policy even if the committee understands the difficulties associated with the rules of the PhD programs and University, (v) to have a clear policy in order to recruit new teams from « outside » and insure the renewal of teams. Moreover, a clear scientific policy and vision is required for the future in coherence with Lyon environment and (vi) to create an International Scientific Advisory Board. This board would not include collaborators from the past 5 years.

- **Production results**

(cf. http://www.aeres-evaluation.fr/IMG/pdf/Criteres_Identification_Ensgts-Chercheurs.pdf)

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	51
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	24
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	51/51
A4: Number of HDR granted during the past 4 years	6
A5: Number of PhD granted during the past 4 years	49

3 • Specific comments on the research unit

- **Appreciation on the results**

It is a pluridisciplinary centre with about 170 persons focused on the understanding of the function of various proteins from the molecular structure to the in vivo function in order to generate bioactive molecules to these targets. In order to achieve such goal, they established well-suited approaches from in silico, in vitro, in cellulo to in vivo. However, the scientific visibility and policy of the institute can be improved. From 2005-2008, the centre published 399 articles. The number of publications increased year after year, but the number of articles published in journals of high impact factor remains too low. During this period, 21 articles had an IF>10, with 16 to speciality. On June 2009, the number of achieved PhD was 47 and the number of PhD students was 47. This is quantitatively excellent.

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

The number of invitations to meetings is variable among the teams. In general it remains too low. Some members got national awards, but it remains not sufficient. Few members were co-organizers of international conferences. Few members belong to editorial boards of journals.

The number of post-docs working in this institute is clearly too low (around 10). There are 4 foreign post-docs at IBCP China (2), Italy (1), Tunisia (1). The PhD students are mainly French.

The different teams are quite efficient to raise money at the regional, national (ANR) and international (EU) levels. The centre is nicely connected with various companies. This is certainly associated with the good number of patents produced between 2005-2008 and emergence of some R&D type of research.

Some teams have nice and long term partnerships with foreign partners. Various teams belongs or coordinates EU program. All teams have at least one foreign collaborator.

One regional TV interview has been given on the cornea project.

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

A director and general secretary are in charge of the common tasks of the centre. The interdisciplinary objective of this center create entropy, which has to be nicely controled. The new organization established in agreement with the various team leaders will theoritically facilitate these interactions among the centre.

The scientific animation and emergence of cutting edge projects is delt with the « Projets de recherche internes multi-équipe ». The goal is to initiate collaboration between teams of the institute.

About half of the permanent staff have high teaching duties. Moreover, they have various responsabilities including Director of Ecole Doctorale, members of CNU, Directors of Masters 1 and 2. This centre is highly involved in teaching. It is also the reason for having a large amount of PhD students in this centre.

- **Appreciation on the project**

The general goal of the director is to allow pluridisciplinarity of the centre with sufficient amount of interactions between the teams. This will be a real challenge because the critical mass is limited (170 persons – 12 teams) and the number of projects is important.

There is a policy about the allocation of ressources. The recurrent resources are shared among the different teams of the centre. Each team is looking for its own resources for the different subjects. The centre promotes new project and collaborative projects using the PRIME system « Projets de recherche internes multi-équipe ». The amount of money is limited but it is certainly a very good initiative.

Such pluridisciplinarity centre may allow the emergence of real cutting edge projects, but it is obviously risky. However, there are already several cutting edge projects in this centre.

4 • Appreciation team by team

Team 1: BIOINFORMATICS: STRUCTURES AND INTERACTIONS (BISI)

Team leader: R. LAVERY

- **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)	4	4
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	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	2	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	4
N7: Number of staff members with a HDR or a similar grade	4	4

- **Appreciation on the results**

This is a team with high competences/activities devoted to understand the links between sequence, structure, interactions and biological functions of different biological macromolecules. Interests of the group cover a wide area of different topics most of them related to structural bioinformatics. Prominent and probably internationally most visible themes of the group are the conformational analysis of DNA and the analysis of DNA-protein interactions where the group has a very strong reputation. Other themes are the analysis of protein-ligand interactions, protein-protein interactions and mechanics of protein folding and stability. In addition, the group continues to provide and develop services like the NPS@ server for the analysis of protein sequences and data bases like the European hepatitis C and hepatitis B data bases. During the last period, the team pursued original researchs, which led to many significant results. In the new configuration, the team will be the most important of the institute in terms of human resources.

Overall, the scientific output of the bioinformatics group is high with almost 50 manuscripts published since 2005. The ratio publications/researchers is good with most researchers publishing well in particular the team leader. Most publications are at a high level in their fields, although publications in the very top journals are lacking. The number of Ph.D. defences during the last period is around 4, including only those directed by people belonging to the new team.

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

The group is internationally recognized. In particular, the team leader is recognized as a world leader in his field with more than 34 invited lectures at international meetings since 2005, co-organizer of international conferences and member of different editorial boards of journals.

Given the number of staff scientists in this team, the ability to recruit students and post-docs could be improved.

The group was able to obtain considerable funding through ANR projects and several other contracts including support from Région Rhône/Alpes.

The group appears in the institute, at the national but also at the international level well connected. The international user community uses the bioinformatics services provided by the group.

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

Three members of the team are involved as Professors/Maitre de Conferences in the L/M/D teaching activities.

- **Appreciation on the project**

The Bioinformatics group pursues a wide spectrum of different themes in the area of structural bioinformatics. Future themes include further development of Web services related to sequence/structure/function analysis, design of new kinase inhibitors, the search of new conditions of enzyme uses to improve chiral synthesis and the understanding of protein mechanics and identifying protein/protein and protein/DNA interactions.

Particularly exciting research directions of the team are the development of improved methods to identify protein-protein interaction partners and the research projects related to understand protein-DNA recognition mechanisms in the cellular context.

- **Conclusion :**

— Summary

The team has a strong integrating role in the institute demonstrated through interactions with many groups. There is an excellent complementarity between the biological themes at the IBCP institute and the scientific interests of this team. The team has a very good scientific production and a good ratio between people and publications. The group covers a broad spectrum of different topics some of them very ambitious. The team greatly benefits of the high expertise and reputation of the team leader.

— Strengths and opportunities

The team is directed by an international leader and therefore has considerable visibility. Some of the future projects are ambitious with the potential to provide important new insights.

— Weaknesses and threats

Because the group covers a broad range of different project there is a considerable risk to become too dispersed in the future. Therefore, some focusing might be required to stay competitive and to have sufficient high impact.

— Recommendations

This team should continue to develop its positive integrating role in the institute. The committee encourages the team to publish in even higher impact factor journals and to attract and transmit its expertise to more young scientists.

Team 2: BIOCRYSTALLOGRAPHY INFECTIOLOGY PROBIOTICS

Team leaders: N. AGHAJARI – P. GOUET

- **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)	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)	4	3
N7: Number of staff members with a HDR or a similar grade	3	2

- **Appreciation on the results**

This research group uses structural biology methods and techniques (mainly X-ray crystallography) in conjunction with bioinformatics, biochemical and molecular biology approaches, to understand the structure and function of proteins of biotechnological and biomedical interest, in particular cancer and infectiology. A major objective is drug design. The group has developed numerous collaborations with internal or external teams to characterize the structure of enzymes of medical interest in fields as cancer, HIV, bacterial virulence, etc... The scientific interests of the group appear very broad, but some of the research topics are poorly connected.

The output of the two team leaders has been good in the last four years. Since 2005 one of the PI has published 10 articles, (4 as last author), the other PI published 26 articles (10 as last author). Overall, the group has published approximately 6 research articles/year/full time permanent scientist, which is very good. However, 13 articles have been published in journals of low IF (<2). The remaining 29 articles were published in good to excellent specialized journals (J. Biol. Chem, Mol. Biol. Evol., Biochem. J.), while obvious highlights are missing.

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

The group appears well connected on the regional and national level, but has only very limited international visibility. Recruitment of scientists, postdocs and students from abroad should be further improved. The team appears very well funded from regional or national calls (22 grants in four years), but apparently has not international funding. A large number of regional and national collaborations, but again, no international collaborations are mentioned.

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

One of the team leaders is Professor at the University with the standard teaching load of 192 h ETD/year. The team also runs the crystallization platform at the institute.

- **Appreciation on the project**

In the future the group plans to focus on themes related to bacterial and viral infectiology taking advantage of the Biopole Centre in Infectiology. Future research plans comprise the analysis of the Ser/Thr kinase Stk1 and their extracellular "Pasta" domains, where interesting first results were already achieved, structure/function relationships of different retroviral integrases, structural analysis of HIV Tat protein and the capsid protein of feline immunodeficiency virus. The proposed research projects are attractive and the overall theme fits well into the local environment. However, especially the retroviral projects are highly competitive and considerable efforts have already been invested by many groups worldwide. Therefore the group might not be able to compete in this area. As a second line of activities the group proposes projects in the area of probiotics and prebiotics. In this project the team plans to develop a collaboration with scientists from INRA (Jouy-en-Josas) to study the interactions of probiotics with the resident flora (including opportunistic pathogen) through the activity of enzymes involved in carbohydrate metabolism. This project appears to be premature as presented. The research of the team on the Ser/Thr kinase Stk1 in particular and on structure/function relationship of infectious processes in general is original and fit well the overall theme of the institute.

- **Conclusion :**

— Summary

This team with a co-leadership emerged from a pre-existing team.

— Strengths and opportunities

This team has a solid structural biology expertise; they solved the three PASTA domains of STK1. The general theme of structure/function relationship of infectious processes can reinforce interactions with other teams. In this context, research on S. aureus STK seems very promising.

— Weaknesses and threats

The team does not benefit of the appropriate environment in virology to be competitive on the HIV-1 project. The project on pre- and probiotics is highly premature and the committee has some serious doubts on its feasibility. The research of this group is highly dependent on external collaborations. The visibility of the PIs is very low.

— Recommendations

The departure of the previous group leader will leave a gap, which will be filled with two internal successors. The committee considers the crystallography as an important activity of the institute and therefore this group has to be carefully monitored. In addition, the group is expected to take advantage of the arrival of the new junior team. Furthermore, the committee recommends focusing on bacterial signalling molecules (eg STK..) and to develop and/or collaborate on functional and genetic assays for testing their structural results.

Team 3: NMR AND HEPATITIS C VIRUS

Team leaders: A BÖCKMANN - F. PENIN

- **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)		
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)	2	
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	3	3

- **Appreciation on the results**

This is a team composed of two groups with high competences/activities in structural analyses. The team works on highly relevant biological questions, mostly related to viral proteins, either as single molecules or in interactions with other partners. A diverse set of methodological approaches, well mastered, is used including liquid and solid-state NMR. The characterization of membrane and fibrillar proteins is a particular challenge and the team is doing very well in progressing in this difficult field. The results obtained in protein purification and structural analysis of fibrillar proteins and of viral proteins are significant, making the team, in its new configuration, very competitive at the international level.

The scientific output of the team is of high quality with more than 60 publications since 2005; a great number of them are published in good/top journals in their fields. One of the two groups, in particular its PI, is engaged in several collaborations that are very productive, but in many cases not as a leader. The ratio pub/researchers is excellent. All the researchers publish well, in particular the two PIs. Considering the new configuration, the number of PhD defenses during the last period is 4, included those in 2010, that is correct relative to the number of people having an HDR.

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

The two groups are internationally recognized. Both team leaders are regularly invited to international meetings to present their work.

The recruitment of PhD and Post-doc could be improved.

The two groups were able to obtain a large number of grants including one ANR and several ANRS contracts.

Several collaborations with French teams have been engaged attested by regular joint publications.

- **Appreciation on the project**

The entire project is coherent, clear and has high level. The different goals are clearly identified. Both groups have the expertise in biochemistry and biophysics (NMR, EM, fluorescence…) to carry out with success all the projects in close interactions with virologists and biologists.

The work of both groups is cutting edge. The use of solid-state NMR for studying membrane proteins in their native lipid environment is particularly of great interest.

- **Conclusion :**

— Summary

The work of these two groups is of high quality in terms of research with international visibility. The team benefits of the experience of the two team leaders and has thus the expertise to carry out this long-term and challenging project, which, if successful, will participate to a high international visibility of the Institute. The publication records and grant acquisitions are at a high level.

— Strengths and opportunities

The team leaders have clearly defined research topics, which make them attractive partners for national and international collaborations. Both are leader in their fields of research, which qualifies them as top people.

— Weaknesses and threats

The team must pay attention to the recruitment of PhDs and postdocs. Lack of sufficient solid-state NMR equipment is a potential threat for this part of the project and a handicap to attract young scientists.

— Recommendations

To be competitive in the long term at the international level, a sufficient access to the 800 MHz wide bore magnet must be a high priority. In spite of the fact that the committee in general does not favour a two-head leadership, in the present case, this structure seems appropriate.

Team 4: PROTEIN PHOSPHORYLATION AND BACTERIAL PATHOGENS

Team leader: C. GRANGEASSE

- **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	1
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	
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)	5	
N7: Number of staff members with a HDR or a similar grade	3	2

- **Appreciation on the results**

This is an internationally recognized group working on the characterization of protein-phosphorylation systems, in particular Ser/Thr-kinases (STK) and Tyr-kinases (TK), in 3 bacterial models (Mycobacterium tuberculosis, Staphylococcus aureus, and Escherichia coli). Their approach is rather straightforward and conventional: search of putative Ser/Thr/Tyr kinases in sequenced genomes, purification and characterization of the kinase activity, structural analysis of the kinases (i.e. phospohrylation sites) and identification of their substrates, construction and characterization of mutants to characterize their biological functions. The final objective is to identify new therapeutic targets that are essential for the bacterial virulence. The team has obtained and published significant and original results during the contract.

The scientific output of this group is excellent/very good, with 38 research publications since 2005 in peer-revewed journals with IF ranging from 13,5 (a collaborative paper in Plos Biology) to 2.2 (Res. Microbiol). There are 6 J. Biol. Chem., 5 be signed by a member of the team as first or/and last authors. Four reviews were published including one in Trends Biochem. Sci. In summary, this group has published approxi. 9 research papers/year/full time permanent scientist, mostly in good to excellent, but not in oustanding journals (except the Plos Biol. paper). The number of PhD defense during the last period is also excellent.

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

The group appears well connected at the regional and national level, but has only very limited international visibility.

Recruitment of scientists, in particular postdocs and students from abroad should be further improved.

The group appears very well funded with 10 grants (or fundings) from regional or national (3 ANR projects and 1 ANR "Jeune Chercheur). This reflects the competivity of the team, although it has apparently no international fundings.

No strong national collaboration (except with S. Nessler, CNRS-Gif) are mentioned although collaborations are already existing through ANR projects. There is no international collaboration.

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

Three members of the team are professor (or associate professor) and have therefore important teaching activities.

- **Appreciation on the project**

This group will stop the work previously carried out on M. tuberculosis and, partly on S. aureus, due to the departure of senior scientists who was in charge of it. They propose to focus on the identification and the characterization of tyrosine kinases of S. aureus and Streptoccocus pneumoniae. This is an excellent choice as the team has the expertise to carry out the entire project.

The research of the team on the Ser/Thr kinase Stk1, in particular, and on structure/function relationship of infectious processes, in general, are original and fit well the overall theme of the institute.

- **Conclusion :**

— Summary

This team will stop working on M. tuberculosis and partly on S. aureus due to the departure of senior scientists in charge of the work. They will focus on the identification and the characterization of tyrosine kinases of S. aureus and Steptoccocus pneumoniae. This is an excellent choice. The team has the expertise to carry out the project. The group leader is promising and it appears to be a good internal emergence.

— Strengths and opportunities

This team has excellent biochemical and structural expertises. They have done an excellent choice of model organisms which are important human pathogens. The organigram of the team presented during the presentation (different from that of the project) is consistent with the proposal as it includes a post-doc trained in the genetics of S. pneumoniae.

— Weaknesses and threats

Unfortunatelly, wide genome analysis of mutants, in particular transcriptomic analysis, are not proposed in the project. They are also clear weaknesses in virulence and cellular studies. The competition will be strong with so important human pathogens as S. aureus and S. pneumoniae.

— Recommendations

The collaborations should be developped with external groups to include relevant wide genomic approaches and virulence studies. The participation to national and international networks are recommended.

Team 5: ABC TRANSPORTERS AND MULTIDRUG RESISTANCE

Team leaders: A. DI PIETRO – P FALSON

- **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)	2	2
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)	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)	6	3
N7: Number of staff members with a HDR or a similar grade	3	3

- **Appreciation on the results**

The research of this team is focused on a biologically important class of membrane proteins, the multidrug ABC transporters and their characterization at the functional and structural level. This work is also medically important because of multidrug resistance to cancer therapy conferred by ABC proteins. The group pursues three major directions. First, the identification of transport specificities and the specific regions responsible for the different specificities followed by homology modelling, site-directed mutagenesis and specific labelling of these regions. Second, identification of small molecules able to abolish cell multidrug resistance and the testing of their in vivo activity. Third, structural characterization of multidrug ABC transporters with the overexpression of different transporters in mammalian cell lines (HEK293, BHK210) and insect cells. Special emphasis is put on the structural characterization of the ABC transporter BmrA where an initial crystal structure at low resolution was obtained. The approaches on functional and structural characterization of three members of this protein family are state-of-the art, as well as the identification of inhibitors. The group has continuously been productive in the last year and plays an important role in this research field.

There is between 4 and 7 publications per year from this group, which is considered as a good, continuous scientific productivity. More than half of the publications are with a first or last author from the group. Although publications are mostly in good international journals, the average impact factor of these journals is relatively low.

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

The group is recognized at the international level as indicated by invitations to international congresses. However, the number of presentations at international meetings and the international visibility could be still further increased (there were only four presentations in four years by the group).

Recruitment of PhD and Post-doc candidates could be improved.

The group has a successful and continuous track record of grant acquisition. Most of the grants are quite small, but there are also a number of substantial grants by ANR.

Currently, most of the collaborations are within France. However, there are also collaborations at the international level (McGill University, University of Firenze and others).

There were four patents filed in the reporting period. This is an extremely high output for such a research team.

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

One member of the team has an active role in organizing and teaching in the biochemistry master program. One of the team leaders serves in several university committees.

- **Appreciation on the project**

The two team leaders present an extensive and informative plan of research for the next four years. It is based on the current approaches and research directions and basically is an extension of present work. All three research projects are feasible and promise to result in a better understanding of ABC transporter function and possible inhibition of transport activity.

The work of this team is original and significantly contributes to relevant scientific questions. A particular strength of the team is its broad methodological expertise that allows them to investigate the multidrug ABC transporters using an original combination of structural biology, biochemical and cell biological approaches.

- **Conclusion :**

— Summary

The work of this team is of good quality, with a good scientific output. On average, publication records and grant acquisition is of a good level, but might still be increased given the high interest and broad relevance of this field of research.

— Strengths and opportunities

The group brings together complementary projects and expertise. The focus on three proteins has a great potential to contribute to significant breakthroughs, e.g. concerning structure determination and identification of inhibitors.

— Weaknesses and threats

The necessity for two group leaders is not obvious to the committee.

— Recommendations

International visibility could be further improved as a function of the quality of the work.

Team 6: MOLECULAR MECHANISMS OF TISSUE REMODELLING

Team leaders: D HULMES – C LETHIAS

- **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+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)	1+1	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+3	2
N7: Number of staff members with a HDR or a similar grade	2+1	3

- **Appreciation on the results**

This team is composed of two groups, which were previously two separate teams from IBCP. They have different expertises, group 1 in biochemical and biophysical fields, and group 2 in cell biology and animal models. The team will be mainly working on matricellular proteins. Their goal is to determine: the regulators of cell cycle modified by tenascin-X; the molecular mechanisms involved in two contexts: tumour invasion and wound healing (skin and cornea). They are also working on thrombospondin 1, a substrate of BMP1 (a tolloid proteinase). During the last period, group 1 pursued original researchs, which led to significant results on molecular mechanisms by which members of the tolloïd family of extracellular proteinases control tissue remodelling during wound repair. They brought also interesting data concerning tissue engineering of the cornea. Using recombinant Tenascine X produced in the team, the group 2 showed that TEN-X participates in the link between collagen fibrils and induces several signalling pathways (Rho, Rac). It also induces cell growth and plays a role in epithelio-mesenchymal transition (EMT).

The team published more than 20 publications since 2005, most of them are co-author papers; a few of them are published in good specialized journals; publications in top journals are lacking. The number of PhD defenses during the last period is 2, that are extremely low relatively to the number of people having an HDR (3).

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

The group 1 is internationally recognized with a team leader who obtained numerous invited lectures at international meetings. Moreover, researchers of this group in national and international meetings have done a lot of oral presentations/posters. The second PI has no international visibility (no invitation); the number of communications by researchers of this group is low and always performed in French meetings.

The recruitment of PhD and Post-doc should be improved.

The first group is able to obtain grants including ANR and European contracts. The second group has obtained few grants principally from LNCC. Their major financing comes from CNRS grants.

Group 1 leader has several collaborations and coordinates an ANR contract "SCAR FREE" (2007-2010) and a FP6 European project Cornea engineering (2004-2007). The number of collaborations of Group 2 leader should be improved.

Group 1 PI has numerous participations in national research committees. Group 2 PI participates rarely in national public or private research committees.

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

Several members are implicated in regional research organization. They are creating a European module on Tissue Engineering.

- **Appreciation on the project**

The projects of the team are the continuations of their previous works. The feasibility at both medium and long term is fine for some parts of the project. However, the project concerning immunity and inflammation is not convincing since they are not experts in the field. The number of topics is too high. In addition, there are many laboratories working in the field.

- **Conclusion :**

— Summary

It is an artificial fusion of two preexisting teams working on two different classes of extracellular matrix proteins. The major concerns of the committee are a lack of coherence between both projects and weak productivity.

— Strengths and opportunities

The past activity of group 1 is recognized internationnally and participates to research networks. The scientific activity of this subgroup is well integrated into the institute. The Tenascin-X project is a medically relevant topic.

— Weaknesses and threats

The number and quality of publications is not sufficient. The project of one group is interesting but the progress is slow. One of the proposed PI has no national or international visibility and never signs as a last author since 2005. Based on the past activity and presentation of the project, the committee has strong doubts whether PI of group 2 can manage a group.

— Recommendations

To have one PI and focus on one project.

Team 7: EXTRACELLULAR MATRIX AND DEVELOPMENT

Team leader: F. RUGGIERO

- **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	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)	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)	4	3
N7: Number of staff members with a HDR or a similar grade	2	2

- **Appreciation on the results**

The research of this group is focused on collagens using modelling, biochemistry, model systems such as mouse and zebra fish. Collagen mutations are frequent in man and lead to disastrous disease. Therefore, research on these important molecules is mandatory. One of the interests of the team is associated with Col X. They performed several studies on this protein including the modelling of N-propeptide, processing of the N-propeptide, identification of binding partners of the N-propeptide, the regulation of angiogenesis by the HepV fragment, the generation of transgenic mice overexpressing the alpha1 chain of Col X. The main originality of this team is to study the role of collagens in zebra fish, which presents several advantages including the ease of imaging during development. For instance they could show that the knockdowns of MMP X induce heart and yolk sac oedema and erythropoeisis defects or knockdowns of Col X induce defects in the perichordal sheath surrounding the notochord and in the craniofacial cartilage. Originally, this team wanted to validate zebra fish has a relevant model. In this respect, they performed a series of knockdown studies collagen genes that have been carried out in the past using the mouse as a model system. They could validate their system but unfortunately, the zebra fish studies remain superficial and did not reveal novel and additional results to the already existing findings from mouse and man.

The team published 26 articles but most of them in rather low rank journals. With a more in depth analysis of the zebra fish studies, particularly when the studied genes have not been analyzed in mouse or human before, the authors should aim for higher rank journals. They have published 4 chapters of books/reviews and they filed one patent. The team has successfully supervised 4 PhD students. All of them have published their PhD work in peer-reviewed journals.

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

The PI is well known in the collagen community for the analysis of novel collagen genes. Since the collagen community consist mainly of biochemists, the work of this team represents also a novel look at collagen biology. Consequently, the PI is frequently speaking at international conferences on ECM. The other members of the teams gave talks in national and international meetings during the past 4 years.

The recruitment of Post-doc must be improved.

A large amount of small grants were obtained during the period. Three fellowships for PhD students, one grant for equipment, five running budgets (four from regions and one from ARC) and one ANVAR in collaboration.

This team has foreign collaborators and belong to informal ECM network

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

In the team, two Assistant-Professors (Maitre de conférence) and one Professor are teaching in L/M/D.

- **Appreciation on the project**

The long term projects are built on the existing work. They are largely descriptive and fail to aim at a mechanistic understanding of the investigated collagens. Furthermore, several proposed hypothesis remain unclear and should be better explained. Furthermore, several collagens will be analyzed in zebra fish, whose phenotypes have already been studied in human disease or in genetically modified mice. Such work would be more appealing if it would aim for mechanistic insights. Furthermore, the team aims at generating transcriptomic analysis but the goal of such work remains vague. Specifically it is unclear why colX or fragments should regulate tumour angiogenesis when the protein and its fragment are highly expressed in tumours. It is also unclear whether the observation of colX as an anti-angiogenic agent has already been studied in the transgenic mice overexpressing an alpha chain of col X. Finally, team will start a completely new project that aims at analyzing Alzheimer disease in zebra fish. The team has hired a new member with experience in studying zebra fish behaviour. It is not clear, however, whether Alzheimer symptoms can be easily assessed in fish and it is also unclear whether fish is a good model system for Alzheimer.

The team established the zebra fish animal model to study collagens in tumour angiogenesis and Alzheimer. The analysis of novel collagens is original, as is the analysis of Alzheimer in fish, It is unclear however, whether it is feasible. The tumour angiogenesis studies are contradictory.

- **Conclusion :**

— Summary

The team is studying several collagens using a range of techniques with a focus on zebra fish genetics. The development of the zebra fish model is complementary to on-going work done in mouse and human genetics and looks very promising, faster and economically interesting.

— Strengths and opportunities

Development of the Animal model. A good expertise for this model, which is useful for other teams in the institute. Good international visibility. The strength of the project is that the study is focusing on an important class of proteins, which could lead to novel findings with a direct impact for medicine.

— Weaknesses and threats

Project aims largely descriptive, in some cases questionable, the zebra fish work often duplicates published work from other animal models instead of focusing on the novel collagens. Tumor angiogenesis project is contradictory. It is unclear whether proposed Alzheimer studies are feasible in fish. Average publication record in low-range journals

— Recommendations

To focus on the novel collagens, which are, not study in other organisms.

Team 8 : EXTRACELLULAR NETWORKS- AGING

Team leader: S. RICARD-BLUM

- **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)		
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)	4	2
N7: Number of staff members with a HDR or a similar grade	2	2

- **Appreciation on the results**

During the project period, the group has worked with central projects related to both the biological/biochemical understanding of molecules important for angiogenesis and the methodological aspects of measuring protein interactions with extracellular matrix components. In particular, the work includes studies by surface plasmon resonance (SPR) to unravel the interaction networks of extracellular matrix proteins and their soluble and cell associated reaction partners. A major emphasis has been given to endostatin, a fragment of collagen XVIII considered to possess an antiangiogenic function. Furthermore, the group has looked into extracellular interactions between collagens, heparin/heparan sulphate and integrins. Interactions characterized include the binding of endostatin to integrins, of heparin/heparan sulphate to collagen V and of endostatin to transglutaminase-2. Furthermore, using SPR array analysis, the group has identified a number of (potential) reaction partners of endostatin and shown that these often include EGF domains. In addition, the group has worked extensively with in silico development of methods and has started the build up of a database of extracellular protein-protein interactions. Although the exact physiological function of endostatin is debated, there is a large interest in this protein fragment and its molecular interactions. Therefore, the interactions of this protein in a purified system will be important information for colleagues working with cell based systems and in vivo. The group has a strong expertise in these measurements and the quality of the results seems to be high. The same holds true for the other protein interactions under study and for the methodological and the in silico work.

The group headed by the second PI in the team has worked with skin elastic tissues with particular emphasis to lysyl oxidase-like enzymes. Particularly, they have studied the role of lysyl oxidase-like 1 (LOXL1) in the cross-linking of elastin and the regulation of expression of LOXL1 in relation to age and various diseases. From a plant extract library, they identified a dill extract that could activate LOXL1 gene expression. They have also studied the expression of lysyl oxidase in keratinocytes and shown that it is absent in basal and squamous skin carcinomas. In studies of the regulation of lysyl oxidase, they showed an upregulation in response to hypoxia in certain cell line(s). To study the causal function of lysyl oxidases in vivo, the group has studied the knockdown of lysyl oxidase isoforms in zebra fish. This study revealed both muscle and neural defects. Finally, this group has studied various skin mechanical properties related to a hereditary skin syndrome (Cutris laxa). The group clearly has a strong expertise in enzymes of the lysyl oxidase family, in their biochemical/biological function and their regulation. The quality of the work and the results seems to be high.

This novel team, formally two independent teams, published 52 peer-reviewed papers during the project period. The team leader is an author/co-author of 18 articles, being either first or senior author for 12 articles. One of the former group leaders is an author/co-author of 14 articles, being senior author for 4 articles. Seven reviews/book chapters were produced. Two articles have an IF>10, in useful position. Fifteen articles have a 10> IF >5, seven of them as first or last author. In general, the papers reflect the same qualities as outlined above in connection with the relevance and originality of the research.

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

The team leader and one staff scientist were invited 25 times to give lectures, some of them in highly recognized places. The various members of the team gave 43 oral communications.

The team has attracted a large number of postdocs, PhD students and students during the 2005-2009 project period, even when considering the fact that it has effectively been the composite of three groups. For the forthcoming project plan, the number recruited so far is considerably lower (4) but since all of these have been recruited recently, it seems reasonable to assume that several new younger scientists will join the group during the forthcoming project.

The whole team has demonstrated a good success rate in the attraction of national and international funding. It should be noted that a relatively large fraction of the funding obtained during the 2005-2009-project period has been granted to a member, who will in the future be heading an independent group. The various members of the team belong to international clusters and have strong international and industrial collaborations.

The build-up of « Interaction » databases, resulting from the team leader work, is a concrete result that may prove very valuable for other researchers. The group leader collaboration with industry also may lead to results for immediate consequence.

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

The background for the fusion of the two groups is questionable since the project overlap is limited.

The team leader has substantial responsibilities in the organization of teaching at the University of Lyon (Coordinator, Master in Biochemistry, etc).

- **Appreciation on the project**

The studies associated with the team leader will continue. They will contribute to the understanding of endostatin´s proposed antiangiogenic function and study new putative roles of endostatin in the brain. As to the first-mentioned function, they will characterize the binding parameters with several established and proposed interaction partners, including various proteins with EGF domains. With multi-domain binding partners, they will identify the binding domain(s) and use available knowledge on the three-dimensional structures of those to suggest details related to binding determinants, based on molecular docking of models. Based on the knowledge about these multiple interactions that they will obtain from these and previous studies, they will attempt to set up a model to explain the effect of endostatin on angiogenesis. They will also investigate various potential molecular binding partners specifically expressed in the brain to look for any interactions that may be relevant in neurodegenerative diseases, including Alzheimer´s disease. In a different project, this group will utilize their expertise in screening and characterization of protein-protein interactions to identify interaction partners of the Leishmania parasite in the extracellular matrix. This is important because the binding to, and transmigration through, the extracellular matrix is a step in the parasite´s infection mechanism. Intact parasites will be subjected to SPR array analyses with numerous immobilized extracellular matrix components. In addition, recombinant parasite surface proteins will be used for SPR analysis. In a collaborative study with external collaborators, this group will contribute to the understanding of hepatitis C virus-induced liver carcinogenesis. The group will characterize the molecular interactions between viral proteins and various extracellular matrix proteins, with particular emphasis to proteins upregulated by TGF-beta. Finally, the group will continue the effort to develop advanced new technology for the measurement of protein-protein interactions and new in silico tools for the rationalization of results, including expansion and refinements of the group´s protein interaction databases.

The second group will focus its studies on the aging and repair of elastic tissues, with particular emphasis to the aging of the skin. This group looks into epigenetic mechanisms responsible for downregulation of LOXL1 (see above), technical aspects of the measurement of tissue elasticity, the role of lysyl oxidase in the terminal differentiation of keratinocytes (including an identified regulatory function of ephedrine therein) and the function of lysyl oxidase in neural differentiation and in neural tumor cell lines.

The projects of the two groups forming this team appear to be realistic and are based on solid expertise.

The projects appear to be reasonable in the light of the available funding, equipment and personnel.

The unraveling of interactions between the Leishmania parasite surface proteins and extracellular matrix components can be considered a cutting edge project.

- **Conclusion :**

— Summary

This team is the fusion of two groups, which were already present in the institute. The fusion is based only on a common protein of interest (Lox) (it is a minor interest for one of the group), which is scientifically questionable. The two merging group(s) have demonstrated a good, to very good, productivity and present a realistic research plan with two projects that should be more integrated. They clearly have the expertise within their fields necessary for the projects planned.

— Strengths and opportunities

One of the group has a strong expertise in the measurement of protein-protein interactions with particular emphasis to extracellular matrix components. This group has also a strong ability to contribute to methodological development within the field and in the creation of valuable in silico tools and databases. Likewise, one of the PI is clearly an expert in the lysyl oxidase group of enzymes and got exciting preliminary results on the function of lox in the neural crest cells derivatives. This PI is involved in national and international network coordination.

— Weaknesses and threats

It may be argued that the sole focus on biochemical and biophysical parameters limits the scope of some of the subjects under study. For example, the identification of the endostatin “interactome” at the protein-protein interaction level might gain strongly from parallel studies with cells or, ideally, studies in vivo. Even though it is appreciated that other investigators may perform such studies based on one of the PI’s publications or database information, an even stronger structure could emerge from direct collaboration. The functional properties of Endostatin are controversial in the angiogenesis field. Scientific interactions between the two subgroups are not optimal.

— Recommendations

They should further persue the functional analysis in the zebrafish model that will also helps for better synergy within the institute. They have to improve internal collaboration. They also should improve the publications in terms of articles in high-impact journals.

Team 9 : CELL / MICROENVIRONMENT CROSS-TALK AND TISSUE REPAIR

Team leader: P. ROUSSELLE

- **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	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2+1	2+1
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)	1	
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	2	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	1
N7: Number of staff members with a HDR or a similar grade	3+1	4

- **Appreciation on the results**

This team was composed of two groups. One group was mainly fundamental and the other one more clinic. At the fundamental level, the team discovered that the G45 domain of Laminin322 could bind syndecan-1 and syndecan-4. This was a major discovery as it was unclear for a long time why Laminin322 requires proteolytic release and degradation of G45. G45-syndecan interaction triggers integrin-independent actin remodelling by Rac and Cdc42 resulting in membrane protrusion and migration. Blocking antibodies against G45-syndecan were developed. They could shown that (i) carcinoma cells produce large amounts of G45 which is retained in the tumour stroma and (ii) that inhibition of G45-syndecan interaction in tumour cells triggers their apoptosis and blocks their migration abilities. The work carried out by this team is original and important. The major findings were published in 2009 in JBC, which is a respectable journal. Beside this paper the publication record is somehow low. The team published several papers in low rank journal. The team leader is often acting as co-author indicating that team leader is frequently invited to collaborate due to her excellent standing in the ECM community.

The second group is mainly based at the University and studies cornea repair.

During the period, more than 60 publications were produced, but only a low number in good position. The team published three book chapters (two)/review (one). Four PhD thesis were defended during the period.

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

The team leader is internationally visible. This is based on previous outstanding research accomplishments (discovery of novel laminins), the current work on G45-syndecan crosstalk and the expertise of Laminin322. The team leader developed several tools (recombinant fragments, antibodies, etc) that are distributed generously to the research community. In light of this scientific reputation the team leader is also invited to international meetings as speaker and holds numerous collaborations with labs in Europe and overseas. Six members of the teams gave 16 talks (9 international, 4 national and 3 consortium). The team leader received two prizes: Prix Pierre Velon, Société Française de Cosmétologie in 2005 and the Prix du cinquantenaire de la Ligue Nationale Contre le Cancer-Comité de la Drôme in 2008.

This team successfully supervises PhD students. The team leader was able to attract an excellent scientist (Research director) in the team, an excellent potential of scientific interactions exist. An ANR contract allows the recruitment of two post-docs. Appropriate advertisement is needed to attract good and motivated young foreigner candidates.

A large amount of grants were obtained during the period, this is excellent. Thirteen running budget grants (three nationals, six foundations, three regions, 1 one Europe), four PhD fellowships, two post-doc fellowships, three CDD for IT.

This team belongs to a European project framework 6 priority 3. Long-term collaborations with a group in Stanford and several other groups in Europe and worldwide.

This team produced 6 patents, 9 MTA and 3 partnerships

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

  — Relevance of the team organization, quality of the management and of the communication policy (optional)

. A very positive point is that the two active groups of this team have a clearly independent profile and still make use of their different expertise in collaborations, which resulted in common publications.

One member of the team is MC.

- **Appreciation on the project**

The team leader is proposing a series of experiments (syndecan binding site on G45; dynamic of GFP-syndecan-1; identification of tyrosine(s) that are phosphorylated upon syndecan-1 binding to G45; identification of syndecan-1 tail binding proteins; G45 recycling upon sybdecan-1 mediated uptake; search for small molecule inhibitors of the G45-syndecan-1 binding) that are highly relevant, well thought through and doable. Some of the proposed experiments have already been initiated and led to first results (tail binders, small molecule inhibitors of the G45-syndecan binding, recombinant syndecans with tyrosine mutations). The discovery of G45-syndecan interaction is highly important for certain cancer cells to survive and migrate and the proposed experiments will lead to important discoveries. Thus the proposal represents a cutting edge project.

The team leader could impressively show that the research performed in the team on G45/syndecan is highly relevant for tissue repair and tumour growth and metastasis.

- **Conclusion :**

  — Summary

Fusion between two preexisting team with complementary expertise to pursue a unique project. The project is important and interesting as it addresses a novel interplay of two signalling pathways. Cell biological and biochemical analyses are sound but could be complemented by in vivo studies.

  — Strengths and opportunities

This team is internationally visible. The recruitment of an expert on intracellular trafficking is very positive. The proposal is very clear, concise, focused. The team's research aims at unravelling an important signalling pathway. They use state-of-the-art technologies, developed numerous tools, are well connected to the national and international ECM communities and successfully applied for research funds.

— Weaknesses and threats

Publications with the team as principal investigator should be improved: increase quality of publications and improve collaborations with other groups in the institute.

— Recommendations

Pursue the project as outlined and improve the quality of the publications.

Team 10: CARTILAGE BIOLOGY AND ENGINEERING

Team leader: F. MALLEIN-GERIN

- **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)	3	2
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
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	3	1

- **Appreciation on the results**

This team works on cartilage and has performed both fundamental and translational research. The group is focused on both the biochemistry, the biology and the biophysical properties of cartilage and has worked with several important projects during the project period. An important aim is to contribute to the development of artificial cell-containing biometrics that can be used for “cartilage engineering”, etc. The group has a strong focus on bone morphogenetic protein-2 (BMP-2) and events regulated by this protein. They have studied the capacity of both BMP2 and TGFb to stimulate cartilage repair. They showed that BMP-2 stimulates chondrocyte differentiation in vitro, as opposed to TGF-beta-1, which rather stimulates a dedifferentiation of these cells. Furthermore, they have identified a new protein, mIFT46 (intraflagellar transport protein) located in the primary cilium of chondrocytes. The gene encoding mIFT46 is regulated by BMP-2 in chondrocytes. mIFT46 was characterized and was shown to be expressed in hypertrophic chondrocytes in the growth plate. Knockdown with siRNA was shown to lead to alteration of gene expression, and morpholino led to embryonic defects in zebra fish. The group has also studied important aspects of the physical state of chondrocyte-containing systems and reconstituted biomaterials. They have demonstrated striking consequences of changes in pressure on the signalling and gene expression patterns in chondrocytes. In addition, they have studied the importance of the physical state of experimental, reconstituted collagen matrices, designed to serve as scaffolds for chondrocyte transplantation. It was shown that the physical state of the reconstituted matrix was decisive for maintenance of the chondrocyte phenotype. The work of the group is a thorough study of a subject that is highly specialized but also very relevant, viewed as translational research. This is an important quality. Not least the striking results of the cellular response to physical pressure is a work of a high degree of originality.

During the 2005-2009 period, the team published 24 articles. Nine of them as first author and thirteen as senior author. Only four articles have an IF>5. The publications appear to be of a high general quality and several papers have been published in competitive journals. A minority of the papers have been published in less competitive but still important specialized journals in the field. Almost all of the papers are focused on the highly specialized group of subjects mentioned above. The group has succeeded to publish a row of in-depth studies, which are likely to be valuable for colleagues in the field. Five theses have been produced within the group. Three of these are quoted as PhD theses and two as "Thèse de pharmacie". This number is low but reasonable for the number of HDR (3). No patent has been reported.

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

The team leader was invited to give six lectures. The various members of the team gave twelve oral communications.

The group has recruited several postdocs, PhD students and students during the 2005-2009 project period.

The group has received substantial funding and has been successful in the establishment of industry collaborations that support the research work. They have several industrial contracts. They also take part in scientific clusters and additional international collaborations. The team leader is co-ordinator of several networks.

The findings of the group have obvious potential for the development of biomaterials that may help future arthritis patents.

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

The team leader takes part in teaching and organization of teaching (Master BioSciences de l´ENS-Université de Lyon).

- **Appreciation on the project**

The new project plan is a logical and promising continuation of the strategy pursued during the 2005-2009 projects. In the next project period, the group will utilize the expertise gained within cartilage development to develop translational research in the field of articular cartilage repair, using cell-containing systems. In addition, they will continue the basic studies on chondrocyte biology. Under the latter heading, they will pursue the function and regulation of the protein IFT46, mentioned above, with particular emphasis to its role in the primary cilia of chondrocytes. It is suggested that this component may take part in "mechanotransduction" in the form of mechanical signals mediated through the cilia. The group has access to IFT46 knockout mice (and also conditional knock-out mice), which should greatly facilitate these studies. In particular, the conditional knockout allele will be utilized for inactivation of the IFT46 gene specifically in mouse chondrocytes. Using these tools, the group will address various questions related to the development of the growth plate and the response of the chondrocytes to mechanical pressure. They will investigate the function of IFT46, the role of BMP-2 in its regulation and the possible involvement of IFT46 in BMP signalling pathway(s). The studies will include global gene expression profiling, protein phosphorylation studies and various histological investigations. Following up on their studies on the response of embedded chondrocytes to mechanical pressure (see above), the group will determine the importance of beta-1 integrins in this relation, and the role of these integrins in the associated signalling events. To this end, the group has access to conditional beta-1 integrin knockout mice. Part of these studies (a transcriptomic analysis) will be performed by an external collaboration partner. As to the translational research projects, the group gives high priority to the setup / improvement of strategies for autologous transplantation of chondrocytes. They will utilize collagen "sponges" as three-dimensional scaffolds for cells, study the use of stem cells instead of chondrocytes and exploit the use of cell stimulation with BMP-2 for cartilage repair. (The latter possibility is controversial, as noted by the group, because BMP-2 may instead stimulate differentiation along an osteogenic line. However, the group has observations supporting the utilization of BMP-2 for chondrogenic cell differentiation). The cell/biomaterial constructs will be tested in nude mice to reveal whether they enable the formation of cartilaginous tissue in vivo. The project appears both highly relevant and feasibility is excellent at both medium and long term, given the expertise of the group. Most of their projects are in continuity with their previous research. The group will include 5 permanents (2

HDR). The strength would be even clearer if it is documented that a fair number of PhD students and postdocs can be recruited.

The elucidation of the role of the primary cilia of chondrocytes and of the mechanisms behind mechanotransduction are cutting edge projects with a considerable degree of originality.

- **Conclusion :**

— Summary

This group has a strong expertise in a specialized but important field. They have demonstrated a good productivity and have designed an important and realistic project following their on-going work.

— Strengths and opportunities

The goal of this team is to develop new therapies. The group has a high degree of specialization and a strong professionalism within the field. The projects fit well into the group's experience and have direct relevance for a defined health problem. The PI is coordinator of several networks and good relationships with companies

— Weaknesses and threats

The low number of students and post-doc is (will be) a major treat.

— Recommendations

High priority should probably be given to the studies with knockout mice, referred to in the project plan, and to the test of new cell/biomaterial constructs in immunodeficient mice. It follows from the note above that it seems important to attract additional young scientists to the group. Efforts should be done to increase the proportion of publications in high impact journals and to patent results should be made.

Team 11: ANTIGEN DESIGN AND MUCOSAL NANODELIVERY SYSTEMS

Team leader: B. VERRIER

- **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)		
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	4	2
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**

The actual team leader joined a former IBCP team in March 2007. From this time, a group within this team was created around two subjects. One was the continuation of previous studies dealing with the design of HIV immunogens for vaccine purpose. The group had successfully engineered viral antigens by site mutagenesis or deglycosylation in order to produce antigenic proteins which may be utilized as components of vaccine candidates. The second part of the work became the major interest of this team and is associated with their future project, it concerns the development of biodegradable nanoparticles with adjuvant function in connection with vaccines. These nanoparticles, based on polylactic acid, were suitable as carriers for several different antigens in vivo, promoting the induction of a humoral response. Altogether the research appears as extremely "applied", constructed as an R&D project in biotech company or pharmaceutical industry. In this regard the major achievements, in the extremely long route conducting to the design of a new vaccine, are in the successful production of antigenic viral proteins and the design of a new vectorisation strategies to target specific cells or cellular compartments for immune intervention. The development of the biodegradable polylactic acid particles as subunit vaccine carrier is certainly original, and a novel vaccination concept. Moreover, this tool is central to several EU projects obtained or coordinated by the team leader. The efficiency of the procedure has already been validated in animal models. The research in its technological aspects, should of course found an appreciable impact in regard of the potential industrial applications, but some other cognitive aspects such as the delivery of antigens through the mucosa, or presentation to DC cells must not be neglected.

The group has a good scientific production. Thirty-four original articles were published since 2005 by the different members of the team in good (J. Mol Biol., J Virol., Vaccine ..) to excellent specialized journals (Blood, J. Immunol.). Nevertheless, It has to be noticed that ten of the articles are signed by a new member of the team and are not related to the topic of this team. Moreover, it appears that most of the publications are derived from collaborationa as the team leader is last author on five articles only. Two patents were produced during the period. The formulation of antigens on PLA nanoparticles as well as the prime boost strategy has been patented (2005, 2007 WO patents). Good implication in scientific supervision during this period.

The team leader possesses a previous industrial experience, which may be an asset for the success of the project. The team is mostly organized around non-permanent young researchers. An effort has to be made in order to stablize the team.

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

The PLA nanoparticles may found numerous applications in the vectorisation for very diverse antigens. One of the force of the team which must be underline is its capacity to gather different competences and partners (including industry) through different international research networks (EU consortium, Munanovac, Cuthivac, Network of excellence (No) Europrise.

Outside the meetings linked to the different EU grants networking, the international impact of the research may appear as limited since two external presentations in international meetings are listed .

Five thesis and one HDR were prepared during the 2005-2009 period. Nevertheless the recruitment appears mostly local.

Excellent ability of the team leader to raise funds (see above). This ability is certainly due to the numerous potential applications of the research, a large number of grants have been raised from industrial, regional, national (ANR) and international (EU) agencies.

Numerous granted national and international collaborations. Undoubtely, one of the strength of the team is its capability to federate research in its field of interest by establishing European networks. The team leader is/was coordinator of several EU projects.

As previously mentionned the work may rapidly find industrial applications (two patents). Two ANR grants have been obtained (PARSYNVAC and ANAVIO) focussing on the industrial development of nanoparticles. Different small companies (PME) are partners of EU networks. For all these reasons, the socio-economic impact of the research may be qualified as high.

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

Before 2007, the team leader was director of a mixed CNRS-industry laboratory. This new team emerged in july 2009 from a former IBCP team. It appears to be managed on the model of R&D team in industry, with clear focus on the different objectives to reach and following an established data management procedure.

- **Appreciation on the project**

The team is now existing in IBCP since July 2009. It is composed of 10 persons (1 research sirector, 1 research ingenior, 3 PhD students and 5 post-docs). The research of the team is in the continuation of the second project. It will concern the formulation and the design of novel biodegradable delivery systems of bacterial/viral antigens to immune cells, for vaccination purpose. More precisely the project aims at designing a mucosal nano-delivery system for the induction of mucosal immunity, by crossing the mucus layer, the epithelial barriers and reaching antigen presenting cells (DC). The project is divided in two distinct parts, the first part is more technical with the elaboration and characterization of multifunctional carriers leading to the immobilization of immunostimulating peptides at the surface of PLA or polysaccharides –made nanoparticles. This part of the work is performed in collaboration with an organic chemistry group (LCP, Marseille). The team will also benefit of the IBCP environment for designing new protein formulations in order to increase the migrating properties of the nanocarriers after coating, such as crystallisation facilities for some viral HIV viral proteins, access to the plasmonic resonance platform and interaction modelling.

The second part of the project address more fundamental questions regarding the transport capacity of the nanoparticles through the mucus and epithelial barriers and immunological related questions such as the mucosal immune properties of coated nanoparticles in relevant infectious models.

The research project is rather built like an R&D project in pharmaceutical industry, than like a fundamental research project. Thus, the opportunity to develop such an project within IBCP remains questionable. Nevertheless, some interactions with other IBCP teams are mentioned but they remain hypothetical, as they were not defined in the frame of a precise collaborative project. Moreover the overall feasibility of the project is higher dependant of numerous external collaborations gathered at that time inside an EU network. In this regard; the long-term viability of

the project is also questionable. The know-how of the group concerning immunology appears limited and should be certainly reinforced to be credible in such a competitive field as new vaccine development.

The proposed new strategy for mucosal immunisation using biodegradables nanoparticles may be considered as a cutting edge advance. For the moment, the real expertise of the team is the conception and formulation of the nanoparticles. The fundamental aspect concerning the crossing of mucosal and epithelial barriers necessitates strong reinforcement in the fields of cellular biology and/or immunology to become realistic.

- **Conclusion :**

— Summary

This team has been implemented in July 2009 and its research project is to design new biodegradable delivery system aiming at targeting mucosal tissues for vaccine purposes. Since 2005, they have developped the use of biodegradable nanoparticles made of poly lactic acid (PLA) as a vaccine delivery platform by using a viral mimetic approach. However, it reads like a startup project without strong biological aims. The group profits from the environment of the IBCP but the advantage of IBCP is still questionable.

— Strengths and opportunities

The project is well-managed and extremely well focused. There is an excellent integration within national and international networks. Excellent fundings.

— Weaknesses and threats

There is no apparent biological question since the research project is essentially technology driven. As presented, it reads like a project from a startup company, being at the interphase of fundamental and applied science. The feasability of the project is highly dependent of numerous external collaborations. For that reason, the long-term viability of the project is questionable. The comity noticed that there is no competence in immunology.

— Recommendations

The development of a start-up company within IBCP would probably be more appropriate to the aims, expertise and qualities of this team.

Team 12: POROS: CHARACTERIZATION AND THERAPEUTIC MANIPULATION OF BCL-2 FAMILY PROTEINS

Team leader: A. AOUACHERIA

- **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
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		1
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
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

- **Appreciation on the results**

The team "Poros" is an emergence of a previous IBCP team. This team has obtained an internal financial support (PRIME). The previous contributions and strength of the team leader are mostly in the fields of bioinformatics, evolutionary molecular biology and phylogeny. His work is mainly focused on cancer and apoptosis. The combination of these different approaches and knowledge is potentially strength in his future work.

This team was just created. The analysis of the publications is not based on the results of a team but on the four staff members; three staff scientists and one IT. Eighteen articles were published between 2005 and 2009, including two review papers, most of them in excellent journals of the field of speciality such as BMC genomics, Mol Biol Evol, Exp Cell Res or Cell Death Diff. The team is on leading position (first and/or last) 14 times (0 : IF>10, 6 : 10>IF>5). The team is on useful position (second or before the last) 1 times (0 : IF>10, 0 : 10>IF>5). Five chapters of books/reviews were written. The bioinformatics effort of the team is also highlighted by the conception of two databases accessible on the IBCP site one concerning "Digipins" the second is a database related to the Bcl-2 proteins family. One PhD thesis was defended during the period. This scored data attest from the high scientific capabilities of this young team.

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

The team leader gave 6 talks; five in meetings (2 internationals and 3 nationals) and 1 seminar in Montpellier. The team leader was a winner of the ARC Young Investigator Award, "bioinformatics and biotechnologies in cancer research", Paris, France. 2005. One article of the team leader (Mol Biol Evol in 2005) was recommended by "Faculty of 1000" Biology.

The team leader was able to attract two young MCF, which were already on site. He participates actively to the formation of young PhD students.

We may consider it as very good according to the age of the applicant. He already got four grants from Associations/foundations (125 k€) and one international grant (11 k€).

There is some international collaboration. This team is just created. We may expect that other collaborations will be established in the near future.

The work peformed by this team may lead to such output. At this point this team got a grant from "Fondation entreprise SILAB".

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

Two members of the team are MC. They were involved in the organisation of one symposium on Pedagogy in 2009.

- **Appreciation on the project**

The project directly relates to the function of mitochondria in the apoptosis pathway, with a special interest for Bcl-2 family proteins physico-chemical properties and their contribution in pro- or anti-apoptotic effects. More precisely the POROS project proposes to establish the structure-function relationship of Bcl-2 family, with a special interest for their membrane-active domains. The project by itself is divided in three parts: 1) the first part proposes to solve the important but very wide biological question related to the molecular mechanisms by which Bcl-2 proteins promote/inhibit apoptosis, 2) the second part of the project is mostly biotechnology-related and propose to develop a new generation of pore-forming peptides, and 3) the last part is related to the bioinformatics know-how of the team and will concern the feeding of the previously created BCL2DB database. The three parts of the project are of unequal importance. The first part of the project by itself raises an important biological question, which will require a broad range of approaches, including cellular and molecular biology, cellular imaging... This part of the project remains poorly defined in terms of cellular models and biological approaches. The only clearly described approach is the biophysical one, which proposes to study the interaction of synthetic peptides with lipid monolayers. Moreover due to the scientific background of the participants, the overall feasibility of this "biological" part of the project remains questionable. The second part of the project appears mainly as an applied project, which may be more adapted in a start-up company and not in an academic environment. The third part of the project is ad equation with the knowledge and competences of the team. Altogether the full project appears to be extremely ambitious in regard of the forces and certainly not feasible in a four-years program.

This new team is financially supported by IBCP direction (PRIME), allocated to a selected an emergent project.

The development of Bcl-2 derived peptides originating from the transmembrane domain of the protein and able to ensure the formation of pores in the mitochondrial membrane, would be of course be considered as a cutting edge project, but it remains very premature.

- **Conclusion :**

— Summary

This group emerged internally after the departure of the previous group leader. The new PI proposes to link his expertise in molecular evolution and bioinformatics to a cell biology question, namely apoptosis. Although the topics are clearly important with a strong medical relevance, it requires a broad knowledge and expertise in different fields of research.

— Strengths and opportunities

Clearly this junior group and its leader is very dynamic, enthusiastic, ambitious and adresses interesting and important topics. Some exciting preliminary results were presented.

— Weaknesses and threats

The committee judges the project very risky and premature particularly for a group lacking the required knowledge and expertise. The committee has some doubts that the proposed group leader has the ability to efficiently manage this project for the time being, in an inappropriate environment.

— Recommendations

A strong mentoring is required to successfully manage a project in the very competitive field of apoptosis. The PI would greatly profit to be in an environment with similar interests. He should apply for competitive young researcher positions (ATIP-AVENIR,..).

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

Team 1: BIOINFORMATICS: STRUCTURES AND INTERACTIONS (BISI)

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+	NN	A

Team 2: BIOCRYSTALLOGRAPHY INFECTIOLOGY PROBIOTICS

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	B	B	NN	B

Team 3: NMR AND HEPATITIS C VIRUS

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+	NN	A+

Team 4: PROTEIN PHOSPHORYLATION AND BACTERIAL PATHOGENS

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	NN	A

Team 5: ABC TRANSPORTERS AND MULTIDRUG RESISTANCE

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	NN	B

Team 6: MOLECULAR MECHANISMS OF TISSUE REMODELLING

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	C	B	NN	B

Team 7: EXTRACELLULAR MATRIX AND DEVELOPMENT

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	B	B	NN	B

Team 8: EXTRACELLULAR NETWORKS- AGING

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	A	NN	B

Team 9: CELL / MICROENVIRONMENT CROSS-TALK AND TISSUE 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
B	B	A	NN	A

Team 10: CARTILAGE BIOLOGY AND ENGINEERING

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+	NN	A+

Team 11: ANTIGEN DESIGN AND MUCOSAL NANODELIVERY SYSTEMS

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	B	A	NN	B

Team 12: POROS: CHARACTERIZATION AND THERAPEUTIC MANIPULATION OF BCL-2 FAMILY PROTEINS

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	A	B	NN	C

Université Claude Bernard Lyon 1

Le Président
Lionel Collet

Villeurbanne, le 29 Mars 2010

M. Pierre GLORIEUX
Directeur de la section des unités de l'AERES
20 rue Vivienne

75002 PARIS

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport du comité de visite concernant l'unité de recherche :

«Institut de Biologie et de Chimie des Protéines» rattachée à mon établissement.

Ce rapport n'appelle pas de commentaire particulier de la part de l'université.

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

Le Président de l'Université

Lionel Collet

Professeur Gilbert DELEAGE
Le Directeur

Answer of IBCP to the AERES report

On the behalf of all the IBCP members, I would like to thank the experts of the committee for their in-depth analysis of our Institute, although we regret that no time was allocated to visiting the labs. We accept the majority of points in the report, however, as director, I would like to make a few general remarks, before some of the groups present factual answers to the comments which specifically concern them.

My first remark is that, although we were very pleased to have been evaluated by a very high level international committee including outstanding foreign researchers from Germany, Switzerland and Denmark, and to have been directly compared with some of the most prestigious institutes in Europe (EMBL Heidelberg, MPI Munich, Zurich University), the obvious differences in both funding and recruiting within the French system were not always taken into account.

Concerning our international attractiveness: there are currently i) 12 post-docs in IBCP, an average of roughly one per team; ii) 13 scientists and technicians hired on fixed-term contracts, iii) 15 foreign PhD students (out of an average total of 40 for IBCP). IBCP has also been able to recruit a total of 12 young researchers during the period 2005-2009 (5 CNRS and 7 University) and to welcome six established researchers from other laboratories.

Concerning our international visibility, during the period examined we had 11 european contracts, three of them coordinated by IBCP members. Our publications have been cited 13,105 times, representing half of IBCP's total citations since its creation. 154 publications (out of a total of 399) were made in collaboration with foreign labs (76 from Europe). Our bioinformatics services also continued to be highly visible on an international level, with, for example, an average of 6500 requests per day to the NPS@ protein sequence analysis server, 75% coming from outside France. IBCP additionally still holds the world record for the largest protein in the PDB determined by solid-state NMR.

We continue to encourage internal collaborations, notably through the PRIME funding we have created. During the last four years, three IBCP teams participated in a single European contract (CORNEA), and three teams are similarly involved in a joint ANR contract. 71 of our publications involve at least two IBCP teams.

During the last four years, I have overseen the restructuring of many of the teams in IBCP in order to introduce a new dynamic and to better exploit the capacities of our interdisciplinary institute. Nine new group leaders have thus been chosen (with co-leaderships in some cases to simplify the transitions). Two of the new leaders are researchers who have recently joined the institute. We have also been able to attract a new group via a highly competitive national program (ATIP, with additional CNRS-INSB support). This success could not be cited in our report since is was only completed at the end of 2009. We will continue our attempts to attract new teams to IBCP, as funding allows, and, notably, thanks to our new building extension (2 floors covering 660 m^2), which will allow us to make an international call for two further new teams.

I would like to make a specific comment on the new POROS team who will make integrative studies of apoptosis regulators, notably developing novel membrane-active peptides. The young leader of this team was recruited by CNRS in 2005 to work in this field and has shown real promise. IBCP offers this team an excellent environment with support in bioinformatics (co-development of the BCL2-database), membrane biology and structural biology (CD, Xray crystallography and solid-state NMR).

Lastly, following the AERES committee's advice, we will set up an international advisory board to provide both evaluations and recommendations for the further development of our institute.

Below are the specific answers of the group leaders:
Team 2: BIOCRYSTALLOGRAPHY INFECTIOLOGY PROBIOTICS

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We have mixed feelings about the comments raised by the committee concerning the biocrystallography group. Please find hereafter the supporting arguments.

"Visibility, attractiveness…": The group, which includes 20% foreigners (including one PI), has two PhD students co-supervised with a German and a Tunisian university respectively. During the four year period examined, members of the group gave 18 invited conferences and 10 oral communications at international conferences and symposia outside France (Japan, Austria, Canada, Slovakia….). We also organised an International Inserm workshop on "Unstructured proteins and related pathologies" and several international meetings (Bratislava, Marrakech…).

The group, and in particular one of its PIs, is engaged in several productive international collaborations (Denmark, Japan, Tunisia, Belgium, Germany), in many cases as a leader, resulting in 26 publications over the period examined.

As concerns the "very low visibility of the PIs", one is an AERES expert and is a nominated member of the CNRS national committee. At the European level, he is a member of the ESRF MX panel in charge of synchrotron beamtime allocation. He also is creator of the web server ESPript performing sequence and structural analyses (1156 citations) for which the academic licence agreement has been signed by 104 laboratories worldwide (Max Planck Institute Dortmund, Institut Pasteur Paris, IRC London, University of Texas Houston, Osaka University ...). The other PI is a nominated member of the French National Biophysics Committee, of the scientific committee of synchrotron radiation FIP/ESRF, and was chosen twice as president of a CNRS recruiting committee. At the international level, she gave nine invited conferences and five oral presentations at international conferences outside France during the last four year period.

"Appreciation on the results and project": We do not understand what is meant by "obvious highlights are missing". Our publications clearly point to obvious highlights, notably in structural enzymology. We appreciate the interest and the support of the committee for the Stk1 project. However, the group has other projects where significant progress has been made. We can cite the partial crystal structure of an ABC transporter membrane protein (mentioned as a highlight for one of the other teams of IBCP) with whom we have a very strong collaboration.

Concerning retroviruses, we agree that structural studies on HIV are very competitive; therefore we chose to focus our efforts on model animal retroviruses, such as FIV, in collaboration with MERIAL, a world-leading animal health company based in Lyon. Once again, our collaborators in this field, in another Lyon laboratory, received favourable comments from their AERES committee for our joint work on avian integrase.

As concerns "probiotics and prebiotics", we agree with the committee that this project is under construction, and indeed it was presented as such. We believe that the expertise we have built up on enzymes producing interesting prebiotics and on membrane protein systems will allow us to progress rapidly in this new and challenging theme.

In conclusion, we remark that the present PI remains active in association with the two PIs who will lead the group in the future. We appreciate that the committee considers the crystallography as "an important activity of the institute". The expertise and visibility established by our group, as well as the creation of an active crystallography platform, serve the institute as a whole and will of particular importance for the development of the new junior team joining IBCP.

Team 6 : MOLECULAR MECHANISMS OF TISSUE REMODELLING

Despite the remarks made by the committee, we believe that the formation of the this new team is a positive move that is motivated by the complementarity of expertise of its members, combined with their common fields of interest. Naturally, the synergy will be strengthened with time (the team was created only six months ago).

While some of our present work extends earlier projects, our fusion has led to new research directions, for example, the proposed work on the physiological consequences of thrombospondin proteolysis. Another example is the role of tolloid proteinases in immunity and inflammation (to be carried out in collaboration with immunologists), which, although involving some risks (as pointed out by the committee) is also very promising.

Team 7: EXTRACELLULAR MATRIX AND DEVELOPMENT

Comments on "Appreciation of the results" and "Weakness and Threats"

« They could validate their system but unfortunately, the zebrafish studies remain superficial and did not reveal novel and additional results to the already existing findings from mouse and man »

During the last four years the team has screened the *in vivo* function of six different collagens in zebrafish among which three were of unknown function. The team has produced new data on the recently identified collagen XXII whose function remains unknown (manuscript in preparation), collagens XII (col12a1 KO in mouse has not been published so far) and XIV (the knock-down of col14a1 in mouse was published in march 2009), and collagen XV, whose gene has two orthologs in zebrafish. From an evolutionary point of view, this represents a particularity novel

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finding. Using zebrafish, the team was also able to provide mechanistic insights, for example, the involvement of *shh* signaling for collagen XV (Pagnon-Minot et al, 2008).
Supporting the importance of these findings, the PI was invited to nine international meetings (USA, Germany, Finland, France) to present the zebrafish work. Several top international laboratories in the extra-cellular matrix field are now using this model for *in vivo* studies (Humphries, Manchester Wellcome-Trust; Paulson, University of Cologne; Greenspan, University of Wisconsin…). Here, as elsewhere, diverse animal models can be very helpful in understanding the multiplicity of pathophysiological disease mechanisms. For instance, the KO of the collagen XVIII gene in mice had no phenotype, whereas mutation of the *col18a1* gene in *C. elegans* was coupled to axon guidance and established a link with the Knobloch syndrome in humans.

« Project aims largely descriptive, in some cases questionable, the zebra fish work often duplicates published work from other animal models instead of focusing on the novel collagens."
Our project focuses on the analysis of the *in vivo* function of new collagens which have not been investigated in mouse models, notably, collagen XXII and collagen XXV.
"It is unclear whether proposed Alzheimer studies are feasible in fish. "
Roughly 100 publications deal with the use of zebrafish in studying neurodegenerative diseases. See the following recent reviews:
1. Transgenic zebrafish models of neurodegenerative diseases.
Sager JJ, Bai Q, Burton EA. , Brain Struct Funct. 2010 Feb 17.
2. The power of the zebrafish for disease analysis.
Ingham PW. , Hum Mol Genet. 2009 Apr 15;18(R1):R107-12. Review.
3. Zebrafish as a new animal model for movement disorders.
Flinn L, Bretaud S, Lo C, Ingham PW, Bandmann O., J, Neurochem. 2008 Sep;106(5):1991-7.
(note that S. Bretaud was recruited by our team in 2007)

Team 11 : ANTIGEN DESIGN AND MUCOSAL NANODELIVERY SYSTEMS
We would like to thank the committee for acknowledging the cutting edge research performed in our group. We have three comments concerning their specific remarks:
1) Our work addresses a clear **biological question**, namely deciphering the mechanism by which nanoparticles carrying drugs and antigens can cross the mucosal barrier. This has been identified as a major challenge in the recent FP7 call *(Summer 2010 - NMP.2011.1.2-2 New therapeutics using nanotechnology to transport macro-molecules across biological barriers).*
2) We are actively building our **interaction with other IBCP** members. Two joint grants (FRM and ANR) have been submitted, and, despite our recent arrival in IBCP, a paper had already been published with the team 2 (Proteins 2010 78(6):1441-56) and others will undoubtedly follow.
3) We appreciate the proposal of creating a **start up**. This proposal has been put into action with the help of the SME PHUSIS since the visit of the committee. We have chosen to create a spin-off with the team leader as a consultant, leaving him enough time to pursue innovative research on the interaction of nanoparticle viral mimetics with mucosal tissue.
Team 12: POROS: Characterization and therapeutic manipulation of BCL2-proteins

"Moreover due to the scientific background of the participants, the overall feasibility of this "biological" part of the project remains questionable." and "The committee judges the project very risky and premature particularly for a group lacking the required knowledge and expertise." and "The committee has some doubts that the proposed group leader has the ability to efficiently manage this project for the time being, in an inappropriate environment."

While we greatly appreciated the Committee's views and suggestions, we wish to draw attention to the following facts. It should be pointed out that the four permanent members of the team are biologists skilled in biochemistry, molecular and cellular biology: the team leader and the two university researchers received doctorates in biochemistry, medicinal chemistry and biology, respectively, and our technician received his degree from the Ecole Pratique des Hautes Etudes (EPHE). The PI has been working for ten years on the Bcl-2 family and has contributed - at the bench - to a number of advances in this field, including the original cloning and characterization of several

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novel proteins. The “cellular models” and “biological approaches” have been abundantly described in the previous papers by the team members and were, in large part, conceived in the IBCP environment. Hence, this young team is not composed of computer scientists who wish to perform biology, but rather of biologists willing to explore new avenues, for which IBCP provides real added value by the use of combined bioinformatics and structural approaches. These are crucial points to consider regarding both the feasibility and advantage of carrying out this project at IBCP. Last, although we fully agree with the Committee that part of the proposed work can be viewed as preliminary, we would like to emphasize that a patent application covering the candidate peptides is pending and that results are currently being submitted for initial publication.

"One article of the team leader (Mol Biol Evol in 2005) was recommended by "Faculty of 1000" Biology."
This sentence should be corrected to "Two articles of the team leader (Mol Biol Evol in 2005 and J Mol Med in 2009) were recommended by "Faculty of 1000" Biology and "Faculty of 1000" Medicine.

Appreciation on the project: *"This new team is financially supported by IBCP direction (PRIME), allocated to a selected an emergent project."*
The POROS team did not receive financial support from IBCP for its establishment. We assume that the financial support mentioned makes reference to a small PRIME grant attributed to the team leader in 2005 for studying collagen evolution in collaboration with other groups of the institute.

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