Centre de biochimie structurale

Rapport Hcéres

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

Section des Unités de recherche

Rapport de l'AERES sur l'unité:

Centre de Biochimie Structurale

Sous tutelle des établissements et organismes:

Université de Montpellier 1

Université de Montpellier 2

CNRS

INSERM

Mai 2010

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

Section des Unités de recherche

Rapport de l'AERES sur l'unité :

Centre de Biochimie Structurale

Sous tutelle des établissements et organismes

Université de Montpellier 1

Université de Montpellier 2

CNRS

INSERM

Le Président de l'AERES	Section des unités de recherche
	Le Directeur
Jean-François Dhainaut	Pierre Glorieux

Mai 2010

Unité

Nom de l'unité: Centre de Biochimie Structurale

Label demandé: UMR CNRS

N° si renouvellement:

Nom du directeur: Mme Catherine ROYER

Membres du comité d'experts

Président:

M. Jean-François MOUSCADET, ENS Cachan

Experts:

M. Jean-Marie RUYSSCHAERT, Université Libre de Bruxelles, Belgique

M. Anton VISSER, Université de Wageningen, Hollande

Mme. Cécile SYKES, Institut Curie, Paris

M. Robin FAHRAEUS, Hôpital Saint Louis, Paris

M. Patrick SCHULTZ, IGBMC, Illkirch, France

Expert(s) proposés par des comités d'évaluation des personnels:

Mme. Ursula LIEBL, Ecole Polytechnique, Palaiseau, membre des CSS de l'INSERM

M. Michael NILGES, Institut Pasteur, Paris, membre du CoNRS

Représentants présents lors de la visite

Délégué scientifique représentant de l'AERES

M. Yves GAUDIN

Représentant(s) des établissements et organismes tutelles de l'unité

Ms. Catherine LABBE-JUILLET, INSERM

M. Thierry MERINNEL, INSB, CNRS

Ms. Viviane LEBOURQ, Déléguée Régionale INSERM

M. Ghislaine GIBELLO, Déléguée Régionale CNRS

M. Jacques MERCIER, Vice-Président, Université de Montpellier 1

Rapport

1 • Introduction

- Date et déroulement de la visite:

The visit took place on January 21st, 2010 and was conducted by an international team of 7 scientists with expertise in the research areas of the 3 teams to be evaluated. The visit started with a general presentation by the head of the lab of the main achievements and the future organization and orientations. Each team leader presented the results and projects and answered to questions. The committee met with representatives from Montpellier University, CNRS and INSERM who stressed the important role of the CBS in the regional and national scientific context. The committee auditioned separately the students and post-docs, the scientists and the technical and administrative staff. A closed-door meeting of the committee to prepare the present report concluded the visit.

- Historique et localisation géographique de l'unité et description synthétique de son domaine et de ses activités:

The Centre of Structural Biochemistry (CBS) was created in Montpellier in 1992 to strengthen structural biology in this region. The CBS activity focuses on structural biology and biophysics to investigate fundamental biological mechanisms, with a strong expertise in NMR and crystallography, and in bioinformatics devoted to the design of new therapeutic strategies. The CBS is an interdisciplinary centre gathering scientists from university, INSERM and CNRS which remained dispersed over several locations until 2006 when all staff moved into a new building that belongs to INSERM. During the past 4 years, the CBS has undergone important changes in permanent staff (15 departures and 9 arrivals) resulting in scientific reorientation for several staff members and a deeply revised organizational chart. Since 2001, the CBS has been recognized as a national resource platform (currently IBISA) based on the unique combination of equipment and expertise. The number of permanent staff is currently 33 persons.

- Equipe de Direction:

The laboratory is headed by Dr Catherine Royer who succeeded Dr Michel Kochoyan (who now acts as deputy director), and is subdivided into three research teams entitled: 1/ Integrated Structural Biology, 2/ Single Molecule Biophysics and 3/ Screening and Structure Based Drug Design. Due to its IBISA label, a transversal organization in technical poles, Biochemistry, NMR and X-ray, Crystallography, and Biophysics, coincides with the teams. A laboratory general committee was elected, which meets on a regular basis to advice and to assist the direction team in all aspects of the laboratory life.

- Effectifs de l'unité: (sur la base du dossier déposé à l'AERES):

	Dans le bilan	Dans le projet
N1 : Nombre d'enseignants-chercheurs (cf. Formulaire 2.1 du dossier de l'unité)	4	4
N2 : Nombre de chercheurs des EPST ou EPIC (cf. Formulaire 2.3 du dossier de l'unité)	22	13
N3 : Nombre d'autres enseignants-chercheurs et chercheurs (cf. Formulaire 2.2 et 2.4 du dossier de l'unité)	0	1
N4 : Nombre d'ingénieurs, techniciens et de personnels administratifs titulaires (cf. Formulaire 2.5 du dossier de l'unité)	16	14
N5 : Nombre d'ingénieurs, techniciens et de personnels administratifs non titulaires (cf. Formulaire 2.6 du dossier de l'unité)	5	3
N6 : Nombre de doctorants (cf. Formulaire 2.7 du dossier de l'unité)	8	6
N7 : Nombre de personnes habilitées à diriger des recherches ou assimilées	14	10

2 • Appréciation sur l'unité

- Avis global:

The CBS has created a unique center for structural biology and biophysics that relies on a strong interdisciplinary blend of biology, biophysics and chemistry. The reorganization for the next 4 years will stimulate the development of innovative methods and tools in the single molecule field by harnessing state-of-the-art, advanced microscopies. The CBS will also continue and reinforce its objective of building an integrated approach for structural biology by extending (and combining) NMR and X-ray methodologies with cryo-electron microscopy. The CBS possesses outstanding instrument resources and central facilities including recently acquired 700 MHz NMR, cryo EM and high-speed AFM instruments with very competent technical staff and young researchers. There is an obvious synergy of the staff research efforts, induced by the open structure of the laboratory inside the building favoring cross-fertilization of ideas and expertise. However, the dispersion of efforts on multiple themes and the absence of high-profile integrated projects (from structure to cell biology and its applications) which may have a significant impact on fundamental knowledge in cell biology has not yet allowed the CBS to exploit so far all of its remarkable potential.

- Points forts et opportunités:

The strengths of the lab are:

1/ Its very strong capacity in developing innovative technologies.

2/ Its multidisciplinary approaches based upon diverse and complementary competencies.

3/ The maintaining by a very competent staff of state-of-the-art instrumentation (recent acquisition of new cryo-EM and 700 MHz NMR) allowing the laboratory to run a national IBISA platform.

4/ A solid funding situation with an impressive capacity to raise money from various sources.

5/ The presence of charismatic lab leaders receiving strong support from the laboratory and giving attractiveness to young scientists.

6/ The successful architectural design of a renovated building where researchers meet constantly; lab space and office space are well organized.

- Points à améliorer et risques:

Main weaknesses:

1/ The low number of graduate students and, to a smaller extent, post-docs.

2/ The new organization and the way the projects are chosen do not really promote internal collaborations despite this being an objective of laboratory.

3/ The lack of technology transfer and the limited number of industrial contacts.

4/ The low visibility at the European level: no organization of student training courses, and/or workshops that would provide access to technologies developed in the CBS

Risks:

The recent decrease in the number of permanent staff creates a risk of impeding the lab to sufficiently maintain a number of technologies, which are too numerous for its human and financial resources.

- Recommandations au directeur de l'unité:

1/ The CBS should better take advantage of its unique gathering of technology and multidisciplinary approach to tackle ambitious biological questions with a continuum from protein structure to biological function.

2/ Internal collaborations should be promoted, especially with the new projects.

3/ The laboratory should focus more strongly on cell biology-driven projects either by developing them in the lab or by extending external collaborations in order to increase the international impact of the work.

4/ The CBS should increase its visibility on the European level in order to attract students, for instance by organizing FEBS practical advanced courses and/or by participating in EU Marie Curie Training Networks. Based upon its strong expertise in biophysics and structural biology, the CBS is perfectly suited to succeed with these initiatives.

5/ The laboratory should adopt a more efficient policy of local collaboration in biology and chemistry.

- Données de production:

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

A1 : Nombre de produisants parmi les chercheurs et enseignants chercheurs référencés en N1 et N2 dans la colonne projet	17
A2 : Nombre de produisants parmi les autres personnels référencés en N3, N4 et N5 dans la colonne projet	NA
A3 : Taux de produisants de l'unité [A1/(N1+N2)]	94,5%
Nombre d'HDR soutenues	
Nombre de thèses soutenues	12
Autre donnée pertinente pour le domaine (à préciser…)	

3 • Appréciations détaillées:

- Appréciation sur la qualité scientifique et la production:

The CBS has a good production with 171 original peer-reviewed articles published in international journals since 2005, among which 85 originated from the lab (first and/or last author belonging to the lab). Major articles of the lab include 1 Nat. Struct. Mol. Biol., 1 J. Cell Biol., 4 PNAS, 5 J. Mol.Biol., 6 JBC, 4 NAR, 4 Biophys. J., 1 JACS, 1 Structure and 1 Langmuir. In addition, laboratory members also contributed to 1 Science and 1 Embo J. and 1 patent was filed during the period.

The laboratory displays therefore a good output. However, given the unique combination of technology available to the teams and the expertise of their members, the primary publications could have been of higher impact if the work had not remained limited to molecular studies, largely of individual proteins.

- Appréciation sur le rayonnement, l'attractivité, et l'intégration de l'unité de recherche dans son environnement:

The Unit has significantly contributed to the emergence of structural biology as a major research axis in Montpellier. Team members have developed numerous collaborations with national and international teams and the lab operates a national platform in structural biology, which solved about ten protein structures for French laboratories since 2005. CBS members organized 3 EMBO practical courses, international meetings on Biophysics and imaging techniques and national meetings in NMR and bioinformatics. There is a great number of invitations to conferences, in particular for the lab head and the senior scientists. The head of the Unit and senior scientists have been invited to give lectures in approximately 90 national and international conferences since 2005. A young member of CBS was awarded the Bronze medal of CNRS 2009 and a young researcher was granted a chaire d'excellence CNRS-Université.

The laboratory is rather attractive for postdoctoral researchers (17 postdocs since 2005, including 8 foreigners), but shows some shortcomings in the recruitment of PhD students, whose number is unfortunately low even with regards to French standards. Conversely, the unit has managed to recruit an expert in electronic microscopy and has attracted two young, promising, scientists who brought new expertise to the lab in particular in the field of singe-molecule imaging and force spectroscopy, thereby demonstrating its very good attractiveness.

The unit has been very successful in raising funds from various sources with participations in 29 research grants among which 18 from ANR grants. However, although several international research contracts have been obtained, the laboratory is involved in only one European project.

- Appréciation sur la stratégie, la gouvernance et la vie de l'unité:

The auditions with the permanent and temporary staff highlighted the very good spirit and atmosphere in the lab. The average age of the technical staff is unusually young for a French lab and of remarkable efficiency. Laboratory life includes regular meetings in English and training activities. Students are particularly encouraged to participate in national and international meetings. Lab members are widely involved in teaching activities. The lab head and several senior scientists are in charge of undergraduate programs. Unfortunately, despite the introduction of specific courses in biophysics, this did not help to attract more PhD students to date.

- Appréciation sur le projet:

The movement of personnel in recent years has led to a major restructuring of the laboratory and to refocusing of its activities. The CBS wishes to reinforce several areas, in particular integrated biology and single-molecule biophysics, which is consistent with its human resources and expertise. The CBS also wishes to reinforce chemical synthesis to provide support for its drug design activity. Although it has a real consistency with the activity of molecular design developed within the lab, it seems difficult to achieve the critical mass necessary to be truly synergistic with the rest of the laboratory. As chemistry is strong in Montpellier, this should open opportunities for collaboration in the medicinal chemistry field.

It is also unfortunate that there is relatively little collaboration with other sites in Montpellier for instance in the field of cell biology, which is strong with many good projects, in the close vicinity of the CBS. From this standpoint, common themes such as microbiology (for instance the Mycobacterium project, single bacteria imaging and kinase pharmacology) irrigate different teams and may thus constitute a basis for more integrated projects.

4 • Analyse équipe par équipe

Team 1 : Integrated structural biology

Team leader : M.Michel KOCHOYAN

- Effectifs de l'équipe ou affectés au projet:

	Dans le bilan	Dans le projet
N1 : Nombre d'enseignants-chercheurs (cf. Formulaire 2.1 du dossier de l'unité)	2	3
N2 : Nombre de chercheurs des EPST ou EPIC (cf. Formulaire 2.3 du dossier de l'unité)	10	5
N3 : Nombre d'autres enseignants-chercheurs et chercheurs (cf. Formulaire 2.2 et 2.4 du dossier de l'unité)		
N4 : Nombre d'ingénieurs, techniciens et de personnels administratifs titulaires (cf. Formulaire 2.5 du dossier de l'unité)	4	6
N5 : Nombre d'ingénieurs, techniciens et de personnels administratifs non titulaires (cf. Formulaire 2.6 du dossier de l'unité)	3	1
N6 : Nombre de doctorants (cf. Formulaire 2.7 du dossier de l'unité)	5	2
N7 : Nombre de personnes habilitées à diriger des recherches ou assimilées	9	4

- Appréciation sur la qualité scientifique et la production:

Team 1 headed by a DR2 CNRS includes 2 DR2 CNRS, 1 CR1 INSERM, 2 CR1 CNRS, 1 PR1, 2 MCU, 4 IRs, 3 IEs and 1 temporary technical staff. This team comes from a major restructuring of former groups that was undertaken to promote a more rational clustering, based on a methodological synergy. This group has developed and operates an integrated platform, gathering extended NMR facilities, X-ray crystallography and more recently cryo-electron microscopy for structural biology studies. The team has employed this platform to solve X-ray structures and studying macromolecular interactions involved in cell signaling, parasites adhesion, bacterial virulence and structure-function of enzymes. Several structures were also solved in the context of internal or external collaborations as part of the platform activities.

The team shows good productivity with 56 papers published over the period. 31 of them directly originate from the team (first and/or last author), most of which with IF>4, and several being published in top journals of the field (1 NMSB, 2 PNAS, 2 Structure, 3 J. Biol. Chem, 4 J. Mol. Biol. 1 NAR). 3 PhDs have defended their thesis during the period under supervision of new team 1 members, and 3 PhDs and 2 postdoctoral students are currently working in the team.

- Appréciation sur le rayonnement, l'attractivité, et l'intégration de l'équipe ou du projet dans son environnement:

The team has obtained 12 research grants from 2005 to 2009 from various sources, including several ANR contracts but no industrial contract or valorization project was reported. The team has several well-established national (Montpellier, Strasbourg, Cachan) and more limited international collaborations (EPFL, Lausanne). One young scientist was hired on a CNRS/University chaire d'excellence. Staff members were invited to give conferences in 13 international meetings and participated in the organization of several conferences and EMBO courses.

- Appréciation sur la stratégie, la gouvernance et la vie de l'équipe ou du projet:

The team has built an attractive multidisciplinary environment with NMR, crystallography and electron microscopy. The interactions within the team are very strong, and it succeeded in compensating several departures due to retirement by an active policy of recruitment. In particular one young assistant professor was hired on a "Chaire d'excellence" allowing the emergence of a novel project.

- Appréciation sur le projet:

Projects are proposed along three axes: First, the structural biology of pathogens, which has several sub-projects including 1. Solving the structure and deciphering the interactions of the complexes formed by the Mycobacterium tuberculosis resuscitation-promoting factor; 2. Investigating the cell invasion machinery of apicomplexes and 3. Determining the structure and interactions of the bacterial nucleoid factor H-NS. Second, developing an innovative multiscale approach combining EM tomography and X-ray diffraction, devoted to studying the mechanism of viral transmission (CaMV, HIV and bacteriophage). And third, undertaking a novel project on the structural biology of the protein degradation machinery (signalosome). There is a fair balance between established projects (Mycobacterium and HNS) and more risky, long-term projects, such as the study of the signalosome regulation. The novel program on multi-scale structural biology, which benefits from the recent arrival of an EM expert, significantly extends the team expertise.

Nevertheless, considering the lack of cell biology and of preliminary data and the fact that it rests on the shoulders of a single young researcher, the signalosome project might be too heavy for a single person to carry out. In order to assure that the project gets all possible chances to succeed, the team should better integrate the signalosome project better with the other CBS-projects and give this project full support. This probably means getting access to cell biology, for example to verify functional aspects of the signalosome subunits.

- Conclusion:

  – Avis:

Team 1 is at the forefront of the integrated biology. It constitutes the historical basis of the CBS and is able to provide a structural support to all biology projects of the laboratory. The team has a good capability of renewing its research topics and building collaborative capacities for reaching its goals. It has recently expanded its technical pole by creating a cryo-EM platform, which allows the development of innovative projects. Among the 7 research projects, three benefit already from specific funding from the ANR and the development of 3D-EM is strongly supported regionally.

However, by getting involved into many lines of research at the same time (viral transmission, signalosome) while wishing to maintain a substantial activity as an open platform, the team takes a risk on difficult subjects. It must therefore ensure that each program is allocated the appropriate, especially human, resources. From this standpoint, most projects are very dependent on either appropriate external collaborations or in-house cell biology development to provide the team with adequate models and knowledge. The feasibility of each project must therefore be carefully evaluated. Finally, the team showed limited involvement in European networks in spite of a real international visibility.

– Points forts et opportunités:

The main strengths of this team are:

1/ A state-of-the art combination of structural biology techniques.

2/ Its attractiveness for scientific staff as it attracted a young scientist who was hired on a highly competitive Chaire d'Excellence CNRS – Université and a senior scientist expert in EM to incorporate this technique in its integrated approach.

3/ The long-term vision of its leader, who is involved in important research management at the national level and whose ideas were pivotal for the creation of the CBS.

– Points à améliorer et risques:

1/ The projects in structural biology are still too focused on single protein structure whereas the team has the potential to address more complex architectures and should take advantage of the fact that the other teams can provide relevant data.

2/ The projects are quite scattered, with a risk not to gather a critical mass of essentially human resources.

– Recommandations:

1/ Tackle more ambitious biological questions.

2/ Pay particular attention to integrating the youngest researcher by giving full support to her project.

3/ Strengthen European collaborations via access to European programs and attract graduate students and postdocs.

Team 2: Single Molecule Biophysics

Team leader: M. Pierre Emmanuel MILHIET

- Effectifs de l'équipe ou affectés au projet (sur la base du dossier déposé à l'AERES):

	Dans le bilan	Dans le projet
N1 : Nombre d'enseignants-chercheurs (cf. Formulaire 2.1 du dossier de l'unité)		
N2 : Nombre de chercheurs des EPST ou EPIC (cf. Formulaire 2.3 du dossier de l'unité)	5	5
N3 : Nombre d'autres enseignants-chercheurs et chercheurs (cf. Formulaire 2.2 et 2.4 du dossier de l'unité)		1
N4 : Nombre d'ingénieurs, techniciens et de personnels administratifs titulaires (cf. Formulaire 2.5 du dossier de l'unité)	3	3
N5 : Nombre d'ingénieurs, techniciens et de personnels administratifs non titulaires (cf. Formulaire 2.6 du dossier de l'unité)		1
N6 : Nombre de doctorants (cf. Formulaire 2.7 du dossier de l'unité)	4	3
N7 : Nombre de personnes habilitées à diriger des recherches ou assimilées	2	3

- Appréciation sur la qualité scientifique et la production:

The team in its current composition arises from a completely new reorganization of the CBS. The team, headed by a DR2 CNRS, includes five other principal investigators (2 DR1 INSERM, 1 DR2 INRA, 1 CR1 CNRS, 1 CR1 INSERM). This is a very strong group focused on biophysical studies of transcription regulation and termination, DNA segregation, membrane assemblies and protein (un-)folding/stability under pressure. The team is actually created around the different single-molecule techniques that have been recently developed. The scientific productivity over the last four years is very good. The scientific contributions amounted to 56 articles, and reviews in top-ranked peer-reviewed journals, of which 30 originating from the team (first or/and last author, including 4 Biophys. J., 3 PNAS, 1 JACS, 2 JBC, 1 J.Mol.Biol., 1 J. Cell. Biol.), 63 invited oral communications in conferences and workshops and 26 invited seminars.

- Appréciation sur le rayonnement, l'attractivité, et l'intégration de l'équipe ou du projet dans son environnement:

Two young lab members have been trained in top groups in the USA (single-molecule fluorescence microscopy and optical and magnetic tweezers) and brought their expertise in state-of-the-art single-molecule techniques to the CBS. Together with the already existing techniques (fluorescence correlation spectroscopy, AFM) the complete technical single-molecule infrastructure gives the CBS a unique position, both nationally and internationally. This is attractive for graduate students and postdocs. The fact that most PIs and other team members are involved in teaching also contributes to the attractiveness. The quality of the team can also be judged from the 19 grants that were acquired from different sources (11 ANR grants), some of which being international funding (COST, HFSP). One young member was awarded the CNRS bronze medal and a second one benefited from an INSERM Avenir program. Finally, although not being faculty staff, several members of this team are involved in teaching regionally, and developed new local training programs in collaboration with Montpellier 1 and 2 Universities.

- Appréciation sur la stratégie, la gouvernance et la vie de l'équipe ou du projet :

The new team 2 is well structured with a very solid base in biophysics articulated around the team leader and the lab head director and several emerging projects developed by young researchers.

- Appréciation sur le projet:

The project comprises four research topics. 1. Single molecule imaging for studying the control of gene expression and of DNA segregation in bacteria; 2. The effect of pressure on protein structure and stability; 3. Development of force spectroscopy methods based on optical tweezers and 4. Development of high-speed AFM and coupling of AFM to super-resolution fluorescence imaging. There is a recent emphasis on single-molecule microscopy beating the optical diffraction limit, which is understandable as it is the only way to look into bacterial systems. The development of high-speed AFM and coupling of AFM to super-resolution fluorescence microscopy is state-of-the-art, although this would likely require additional research staff as the AFM expert of the laboratory is going to retire in the near future.

- Conclusion:

  – Avis:

The team 2 is obviously a leading group in biophysics in France. While maintaining an outstanding expertise in its historic domains such as biophysics of membranes and fundamental studies in the field of the effects of pressure on protein structure, the team has reinvented itself significantly with innovative projects in the field of the single-molecule imaging. New contributions have been made for example with the monitoring of the movement of isolated molecules during transcription with a resolution of 200 Å. Considering the numbers of young researchers, this is a very promising team as an ensemble.

– Points forts et opportunités:

1. The attractiveness of this team for new young talented scientists in the last 4 years.

2. The opportunity has been taken in hiring young promising people on new subjects that enrich the lab's technical spectrum and subjects.

3. The excellent expertise of the team leaders at an international level.

– Points à améliorer et risques:

1/ The team encompasses 4 groups that do not seem to share much of the scientific approaches.

2/ Despite its outstanding expertise in biophysics and fluorescence imaging, there is a certain absence of applications on the cell biology side as witnessed by rather specialized publications. It must be admitted, however, that some studies can only be carried out with isolated biological molecules.

3/ The DNA segregation subject was brought by a young PI from his former laboratory, which represents a risk of project limitation. However, the team is aware of this potential pitfall and one can therefore expect this project to lead to new exciting developments.

– Recommandations:

1/ Develop original projects on the high-speed AFM and reinforce this activity in collaboration with other techniques in the lab.

2/ Enhance visibility at the European level by participation in EU Marie Curie Training Networks and by organizing FEBS advanced practical and lecture courses.

Team 3: Screening and Structure-based Drug Design

Team leader: M. Gilles LABESSE

- Effectifs de l'équipe ou affectés au projet (sur la base du dossier déposé à l'AERES):

	Dans le bilan	Dans le projet
N1 : Nombre d'enseignants-chercheurs (cf. Formulaire 2.1 du dossier de l'unité)	2	1
N2 : Nombre de chercheurs des EPST ou EPIC (cf. Formulaire 2.3 du dossier de l'unité)	5	4
N3 : Nombre d'autres enseignants-chercheurs et chercheurs (cf. Formulaire 2.2 et 2.4 du dossier de l'unité)		
N4 : Nombre d'ingénieurs, techniciens et de personnels administratifs titulaires (cf. Formulaire 2.5 du dossier de l'unité)	3	2
N5 : Nombre d'ingénieurs, techniciens et de personnels administratifs non titulaires (cf. Formulaire 2.6 du dossier de l'unité)	1	
N6 : Nombre de doctorants (cf. Formulaire 2.7 du dossier de l'unité)	5	2
N7 : Nombre de personnes habilitées à diriger des recherches ou assimilées	5	3

- Appréciation sur la qualité scientifique et la production:

Team 3 is headed by a DR2 CNRS and includes 1 DR2 CNRS, 1DR2 INSERM, 1 CR1 CNRS, 1 CR1 INSERM, 1 MCU, 2 IR2 CNRS, 1 IE CNRS and 1 TCN CNRS. The former team was devoted to the screening and rational design of active compounds. Most of its activity was devoted to the development of new methods for virtual screening. The team interacts significantly with team 1 as it has developed in silico methodologies within the context of the IBISA platform. Successful methodological developments in bio- and chemo-informatics (3 software servers and 2 databases were set up by team members) have also attracted a number of external collaborations through the team's platform activity. The new organization now includes a biology group with a particular focus on nuclear receptors as biological targets. Other targets include cyclophilins, kinases and virulence factors for which the team has established external

collaborations. There is a good publication output with 59 articles in international peer-reviewed journal and 4 reviews, of which 35 originating from the team (first and/or last authors, including 2 JBC, 3 J. Med. Chem. 3 NAR, 2 PNAS, 1 J. Chem. Inf. Model, 3 J. Mol. Biol., 1 Structure, 1 EMBO rep). Senior scientists were invited to give lectures in 10 national (4) and international meetings (6).

- Appréciation sur le rayonnement, l'attractivité, et l'intégration de l'équipe ou du projet dans son environnement:

The team has obtained 8 research grants from 2005 to 2009 from various sources, including 2 ANR contracts "blanc" and one very competitive Young investigator ANR grant for the fragment-based inhibitor design project. Staff members were invited to give conferences in 10 national or international meetings and participated in the organization of two conferences on bioinformatics. One 'CIFRE' fellowship was obtained in collaboration with a small company, thus demonstrating the potential of the team for private collaborations. However this has not translated into further collaboration to date.

- Appréciation sur le projet:

The team proposes three complementary research projects. 1/ The goal of the first project is to develop and provide access to a bioinformatics platform allowing extensive *in silico* analysis of proteins sequence and structure. A particular emphasis is put on building an efficient interface between bio- and chemo-informatics, allowing for instance comparative docking on vast families of proteins; 2/The second project is dedicated to the design of new pharmacologically active compounds. As during the previous period, the compounds will be generally synthesized by partner laboratories. There is some in-house synthetic chemistry aiming primarily at obtaining fluorescent probes for biophysical characterization of interactions with targets that are relevant for the laboratory. 3/ The third project concerns the function of nuclear receptors with the addition of new objectives consisting in designing inhibitors of the enzymes involved in the epigenetic regulation of these receptors.

- Appréciation sur la stratégie, la gouvernance et la vie de l'équipe ou du projet:

Team 3 results from the merging of 3 groups. This grouping was based on previous collaborations and on the prospect of expanding biological applications. Team 3 is now quite well balanced with the presence of complementary competences combining structural biology, bio-informatics and some organic chemistry. The three teams have different focuses on aspects that can lead together to new rational drug design. The fragment based drug design in combination with *in silico* modeling is an attractive model that has the potential together with chemistry to lead to identification of novel protein interacting compounds. The obvious target for this group is the nuclear receptor for which the team harbors a leading expert. As this model system becomes tested and reaches its full potential the team should generate industrial interest. As the approach becomes tested and validated, stronger collaborations with other groups of the CBS are likely to develop. The bio-informatics is already a widely used tool for protein analysis and is helping in- and out- of house researchers.

- Conclusion:

  – Avis:

Recent successful methodological developments in bio- and chemo-informatics have attracted a number of external collaborations through the team's platform activity and constitute an important service to the interested scientific community. The interesting project on nuclear receptors pharmacology, based on proprietary results allowing the team in participating in a European training network (ITN) is a good opportunity for the team to increase

its visibility and to attract funding as illustrated by the recent efforts in submitting applications related to this project. The somewhat limited industrial interest despite the focus on medicinal chemistry is a point of concern, as is the evolution in synthetic organic chemistry.

- Points forts et opportunités:

The main strengths are:

1/ The service that the bioinformatics teams makes to the national community

2/ The presence of diverse and complementary competences within the team, combining structural biology, bio-informatics and organic chemistry.

3/ Its state-of-the art instrumentation.

- Points à améliorer et risques:

1/ The limited industrial interest despite the focus on medicinal chemistry is surprising.

2/ The epigenetic project, although a logic extension of the existing research, carries a considerable risk in such a competitive field, as it benefits from merely one post-doc, which seems insufficient to make an effective contribution.

3/ The goal to design and produce pharmaceutical compounds is only with difficulty compatible with the limited synthetic organic chemistry potential within the lab, which is not compensated by local collaborations, despite the presence of strong chemistry lab in the environment in Montpellier.

- Recommandations:

1/ The organizational problem with the synthetic chemistry activity must be solved to secure the future of this activity. To that effect internal collaborations should be reinforced to focus the activity on biological targets of interest for the other teams and external collaborations must be sought or extended to increase the chemistry resources available to the team.

2/ Critically reassess the epigenetic enzymes project whether it can succeed in the international competition without allocating more resources.

3/ Improve the strategy concerning patenting and actively look for industrial links

4/ Reinforce collaborations both within the team and with the other groups of the lab.

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

Nom de l'équipe :INTEGRATED STRUCTURAL BIOLOGY

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	A+	A

Nom de l'équipe : SINGLE MOLECULE BIOPHYSICS

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

Nom de l'équipe : SCREENING AND RATIONAL DESIGN OF THERAPEUTIC MOLECULES

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

Université Montpellier 1

Montpellier, le 10 mars 2010

Le Président
Ph A : NG
Départ 2010 - 72

Monsieur Pierre GLORIEUX
Directeur de la section des unités
de recherche
Agence d'Evaluation de la Recherche et de
L'Enseignement Supérieure (AERES)
20, rue Vivienne
75002 PARIS

Monsieur le Directeur,

Je m'associe aux remerciements formulés par l'ensemble de la direction de l'unité de recherche **«Centre de Biochimie Structurale »** pour la qualité du rapport d'évaluation fourni à l'issue de la visite du comité d'expertise.

Au titre de l'établissement, le Vice Président du Conseil Scientifique et moi-même n'avons aucune remarque particulière à formuler en complément de celles exprimées par le Directeur de l'unité dans les documents joints à ce courrier.

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

Philippe AUGE

5, boulevard Henri IV – CS 19044 – 34967 Montpellier cedex 2 – Tel : 04.67.41.74.00 Fax : 04 67 41 74 56

Réponse du Directeur du CBS rapport de l'AERES sur le Centre de Biochimie Structurale, Unité mixte INSERM, CNRS, UM1 et UM2.

Réponse aux commentaires du comité de visite AERES au CBS

Tout d'abord, nous remercions le Comité d'experts AERES pour la qualité de l'analyse effectuée et la pertinence de ses recommandations. Le rapport du comité souligne un certain nombre de points sur lesquels nous allons centrer nos efforts en prenant en compte leur avis, mais pour lesquels nous souhaitons aussi ici préciser nos efforts passés et actuels, ainsi que les atouts du laboratoire pour relever ces défis. Comme le note le Comité AERES, le CBS est performant et attractif, mais il n'a pas encore atteint son plein potentiel. Le centre est effectivement en cours de renouveau important depuis le dernier quadriennal puisque nous avons vu un roulement de plus de 50% et une baisse globale de 26% de nos personnels permanents.

Le comité a fait un certain nombre de remarques et observations concernant l'intégration et la signification de nos travaux.

"However, the dispersion of efforts on multiple themes and the absence of high-profile integrated projects (from structure to cell biology and its applications) which may have a significant impact on fundamental knowledge in cell biology has not yet allowed the CBS to exploit so far all of its remarkable potential.

"The recent decrease in the number of permanent staff creates a risk of impeding the lab to sufficiently maintain a number of technologies, which are too numerous for its human and financial resources."

"The laboratory should adopt a more efficient policy of local collaboration in biology and chemistry".

"The CBS should better take advantage of its unique gathering of technology and multidisciplinary approach to tackle ambitious biological questions with a continuum from protein structure to biological function".

"The laboratory should focus more strongly on cell biology-driven projects either by developing them in the lab or by extending external collaborations in order to increase the international impact of the work."

Nous voudrions soulever trois points en réponse à ces commentaires et ces recommandations.

1. Premièrement, nous sommes conscients de l'excellent environnement en biologie et des grandes ressources en chimie qui nous entourent à Montpellier. D'ailleurs, nous entretenons déjà des collaborations étroites avec nos collègues des instituts biologiques locaux qui ont permis la publication de 25 articles en 4 ans. En revanche, la mise en place de collaborations concernant un grand sujet de biologie cellulaire intégré, de la structure et la dynamique structurale jusqu'à la biologie cellulaire, est un processus plus long qui est en cours. Nous avons entamé des discussions avec nos collègues des instituts de biologie sur la meilleure façon d'intégrer notre savoir faire et nos perspectives à leur problématique biologique. Elles ont permis de définir deux stratégies que nous comptons mettre en place. Tout d'abord nous pourrions profiter de notre besoin de recruter de nouveaux chercheurs (PI) en biologie structurale (RMN, AFM, RX, ME) pour **cibler ces recrutements dans les domaines de la biologie structurale et la biophysique de la chromatine (IGH) et du cycle cellulaire (CRBM)**. Pour aider à ces **recrutements « conjoints et ciblés»,** il serait utile de pouvoir les baser sur des **postes fléchés**. Par ailleurs**, l'attractivité d'un tel** poste serait plus importante aussi bien pour le chercheur que pour les deux laboratoires concernés si la personne recrutée bénéficiait d'une **double affectation** (CRBM/CBS par exemple). Ceci est courant dans les universités américaines (joint appointment) et s'avère être un outil important dans le recrutement. Notre seconde idée est d'organiser des journées récurrentes et

conjointes de présentations scientifiques entre nos instituts. Les premières réunions sont prévues ce printemps.

2. Le deuxième point concerne la signification et l'intégration des sujets du CBS. Contrairement à ce qui est noté dans le rapport, il n'y a pas une «absence of high profile integrated projects from structure to cell biology and its applications ». Un exemple d'un tel sujet est celui des récepteurs nucléaires qui sont étudiés au laboratoire depuis plusieurs années. C'est un projet intégré (5 PI's aux compétences très variées et plusieurs collaborations externes locales, nationales et internationales) qui combine cristallographie, biologie cellulaire, chimie, fluorescence et bio-informatique structurale, et qui a donné lieu à 10 publications en 4 ans (dont 2 en 2010) dans d'excellentes revues (entre autres, *EMBO Reports, Chemical Biology, PNAS, JBC* et très récemment *NSMB*). Ceci étant dit, nous allons continuer de concentrer nos efforts sur ces sujets de grande signification pour augmenter encore notre efficacité.

3. Enfin, une clarification sur nos interactions avec les laboratoires de chimie de Montpellier nous semble nécessaire. Les membres de l'équipe 3 (dont un chimiste médicinal) entretiennent des collaborations très étroites, très productives et depuis très longtemps (~10 ans) avec des équipes de chimistes locales, nationales et internationales. Néanmoins, tout comme un laboratoire de biophysique ou de biologie structurale a besoin en interne de la biochimie préparative pour ne pas peser trop lourdement sur ses collaborateurs externes, nous aurions besoin d'une petite capacité en chimie de synthèse pour des sondes spécifiques à notre travail, ou des ligands ponctuels à tester. Cette activité de routine en chimie de synthèse ne doit pas être confondue avec les programmes intégrés de recherche de composes actifs que nous poursuivons avec nos collaborateurs.

Un second sujet sur lequel le comité a fait des commentaires et recommandations est celui de notre manque de visibilité au niveau européen.

« The low visibility at the European level: no organization of student training courses, and/or workshops that would provide access to technologies developed in the CBS."

"The CBS should increase its visibility on the European level in order to attract students, for instance by organizing FEBS practical advanced courses and/or by participating in EU Marie Curie Training Networks. Based upon its strong expertise in biophysics and structural biology, the CBS is perfectly suited to succeed with these initiatives."

Bien qu'étant loin d'être inconnus au niveau Européen comme en attestent nos contrats collaboratifs ou postdoctoraux, l'organisation de plusieurs colloques et le nombre d'invitations dans des congrès en Europe, il est clair que notre implication et notre visibilité Européennes pourraient être nettement plus importantes. La suggestion d'organiser un atelier FEBS de Biophysique donnant accès aux technologies développées au CBS est excellente et nous la suivrons à la lettre. Par ailleurs, nous avons plusieurs demandes de subventions européennes (ITN, ERC) actuellement en cours.

Le dernier point auquel nous voudrions répondre concerne les collaborations internes au laboratoire. Le comité a remarqué:

"The new organization and the way the projects are chosen do not really promote internal collaborations despite this being an objective of laboratory." and "Internal collaborations should be promoted, especially with the new projects."

Nous sommes réellement surpris par cette conclusion. Premièrement, la nouvelle organisation ne diffère pas beaucoup, structurellement parlant, de l'ancienne. Nous avons toujours considéré chaque chercheur du centre comme étant indépendant, et libre de collaborer avec ses collègues. Beaucoup l'ont fait et le font toujours. Ainsi, des publications citées dans le rapport, 30 sont le résultat de collaborations entre PI's du laboratoire. Actuellement, il existe 10 collaborations entre les PI des différentes équipes et 20 collaborations à l'intérieur des équipes, ces derniers impliquant souvent des développements méthodologiques.

Le comité insiste surtout sur l'importance des collaborations pour les nouveaux projets. En ce qui les concerne:

1. Un jeune chercheur travaillant sur la biologie structurale de *M. tuberculosis* est arrivé il y a ~ 4 ans. Il a su établir des collaborations avec ses collègues pour l'aider à réussir son projet (6 publications de haut niveau, dont *NSMB, Structure* , 2 *JBC* et 1 brevet).
2. Un autre jeune chercheur, recruté au laboratoire en 2008 co-encadre la doctorante d'un collègue. Il collabore aussi avec le groupe de cryo-ME sur son sujet principal, et avec ses collègues en biophysique sur les nouveaux développements.
3. Un troisième jeune chercheur, expert en cryo-EM arrivé en 2008, collabore déjà avec plusieurs collègues, bien que le microscope n'est opérationnel que depuis 5 mois.
4. Enfin, une jeune chercheuse, arrivée en Octobre 2009 collabore sur son sujet avec deux membres de l'équipe 3 et bénéficie de la collaboration de plusieurs ITA. Une collaboration en cryo-ME sur les grands complexes est prévue.

Depuis toujours, les forces du CBS se sont concentrées sur les projets les plus productifs. Ceci a été vrai dans le passé pour des récepteurs nucléaires mentionnés ci-dessus, ainsi que pour les régulateurs bactériens (7 publications en 4 ans impliquant 7 PIs (dont 2 RMNistes, 1 cristallographe, 1 biochimiste, 2 biophysiciens), 2 IR, 2 doctorants, et 2 post-doctorants.) A l'avenir, notre intention est de continuer de nous focaliser sur les sujets les plus porteurs, y compris ceux de nos nouveaux arrivants et ceux en collaboration avec nos collègues biologistes montpelliérains.