AFMB - Architecture et fonction des macromolécules biologiques

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Architecture et Fonction des Macromolécules Biologiques (AFMB) – UMR 6098

From the

CNRS

Université de la Méditerranée

Université de Provence

January 2011

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

January 2011

Research Unit

Name of the research unit: Architecture et Fonction des Macromolécules Biologiques (AFMB)

Requested label:

N° in the case of renewal: UMR 6098

Name of the director: M. Yves BOURNE

Members of the review committee

Committee chairman

M. Jean-François MOUSCADET, ENS, Cachan

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Le membre du CNU n'a pas pu se déplacer.

Report

1 • Introduction

- Date and execution of the visit

The visit took place on January 24th, 2011 and was carried out by an international team of 7 qualified scientists with complementary expertise in the research areas of the 7 teams evaluated. The visit started with a general presentation of the laboratory by its director, its history and achievements and the past and future organizations. The team leaders presented their results and projects and answered to questions of the committee. One group leaving the AFMB was given the opportunity to present its results in a closed-door meeting. Committee members met with the CNRS and University Aix-Marseille 2 representatives, the PhDs and postdocs, the technical staff and the scientists. After a final meeting with the senior management of the laboratory (director and deputy director), the committee gathered on January the 25th to establish the present report.

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

The Laboratory "Architecture et Fonction des Macromolecules Biologiques" (AFMB) is located on the Marseille Luminy Campus where it moved in 2005. Since 2008, the laboratory has occupied 1800 m2, which are split over two buildings. Until 2010, AFMB was subdivided in 8 teams, of which 7 are renewed for the 2012-2017 project and one is leaving the AFMB, and two departments, (Structural Biology and Structural Virology). These departments were designed to bring together the teams located respectively in the AFMB main building and in the adjacent ESIL building on the campus. To improve the interactions between the teams, this division in departments has been now abandoned in favor of redesigning 7 teams with a better coherence.

- Management team

Yves Bourne who succeeded Bernard Henrissat in 2008 and is assisted by Bruno Canard as deputy director heads the laboratory. Yves Bourne was reappointed for the next period in charge of the new project. A laboratory board and a team leader board that meet on a regular basis, complete the management organization.

- 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)	6	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	15	17
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	9	9
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	17	17
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	12	9
N6: Number of Ph.D. students (Form 2.7 of the application file)	13	11
N7: Number of staff members with a HDR or a similar grade	16	19

2 • Overall appreciation on the research unit

- Summary

Since its establishment, the AFMB has succeeded in setting up an outstanding center for structural genomics that has yielded significant successes in glycobiology and infectious agents, while allowing the development of a world-leading expertise in glycogenomics. Under the leadership of its successive directors, the laboratory has demonstrated a strong reactivity that facilitated the early development of a protein production platform, the productivity of which, being now well established, raises the possibility for the lab to extend its activities toward more integrated studies in the fields of glycobiology, virology and immunology. This evolution might bring benefit to all areas of research of the lab including glycogenomics, provided that a critical mass of resources be allocated to the different projects. This reorientation is accompanied by a restructuring with the arrival of a senior researcher in neurobiology, the creation of a young team in structural immunology and the reorganization of the department of structural virology with a novel emphasis on medicinal chemistry. This latter point capitalizes on the recent creation of a second platform, now part of a national facility for the design and development of novel antiviral compounds. The recent integration of AFMB into regional structures dedicated to infectious diseases offers obvious opportunities for this diversification. Nevertheless, the small teams that result from bringing together PIs with different backgrounds and expertise display scientific and technical vulnerabilities potentially threatening their future, and demanding therefore in-depth consideration. Besides, the AFMB also enters a period that will see the departure of prominent scientists, the replacement of whom must be carefully planned.

- Strengths and opportunities

The strengths of the labs are:

1/ A strong capacity for project renewal by addressing timely questions aimed at tackling difficult subjects.

2/ The implementation and maintenance of state-of-the art platforms in structural genomics and antiviral drug design.

3/ The presence of international scientific leaders in structural and genomic biology, and their complementary expertise (glycobiology, virology, immunology) resulting in a very strong attractiveness of the lab for young researchers and in opportunities for international collaborations.

4/ A world-class expertise in glycogenomics arising the development of a unique database with global leadership.

5/ An impressive funding situation, which is already secured for most future projects thanks to national and international grants.

6/ The strong support of both CNRS and associated Universities, which may create opportunities for extending the laboratory facilities.

- Weaknesses and threats

The main weaknesses and threats are:

1/ A certain lack of attention paid to the valorization of research, particularly in getting intellectual property for very original results, despite industrial contacts.

2/ A redistribution of teams, in particular the smallest ones, which is not necessarily optimal and may mask inequalities or inconsistencies that should be discussed over for the future project period.

3/ The future of the CAZy database which should be carefully positioned/supported to maintain its current visibility and international significance.

4/ The position of organic chemistry components within projects, the scale of which should be adequately thought out and sized to optimize the making of a real impact in the antiviral development field.

- Recommendations

1/ Reinforce the potential in glycogenomics.

2/ Reconsider the objectives of the small teams.

3/ The laboratory, in particular in the structural virology part, should focus on few high-profile projects either by developping an in-house cell biology expertise or by establishing strong collaborations in order to exploit the results for high impact publications.

4/ Adopt an efficient policy of collaborations in chemistry.

5/ Attention should be made to the maintenance of platform in relation to the recruitment of temporary technical people whose future job opportunities are not clear.

- Production results

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

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	6
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	15
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	1
A4: Number of HDR granted during the past 4 years	5
A5: Number of PhD granted during the past 4 years	17

3 • Specific comments

- ## Appreciation on the results

For the 2006-2010 period, lab members have published 264 publications in international journals (average IF: 5,9), of which 129 originating in AFMB (first and/or last author). 17 publications have an IF>10 (of which 1 NSMB & 1 Curr. Opin Struct Biol originated in the lab, and 2 Science, 4 Nature, 2 Nature Meth., 5 Nature Biotechnol., 1 Neuron were as collaborative works). In addition, 5 patents were filed during the period. The AFMB has therefore an excellent production. Nevertheless, given the stunning expertise and technology facilities available to its members, the laboratory has the means to further increase the visibility of some of its fields of research, by focusing on integrated studies (from structural to functional studies) with a potential for publication in the world's leading journals.

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

The laboratory is the flagship of structural biology in the Marseille region and belongs to the small circle of French leaders in this field as evidenced by the association of AFMB in major French infrastructure projects. Among those labs, AFMB holds a special position in the field of structural genomics that it contributed to create in France. AFMB is also a unique laboratory in the field of glycogenomics in which AFMB is a world leader. This position allows the lab to occupy an important place in collaborative international networks. AFMB is the core laboratory of several European networks in the area of the structural genomics and virology (SPINE, VIZIER, EVA). More than 120 collaborations throughout the world were enumerated. The most developed collaborations have resulted in obtaining two international programs from CNRS with Singapore and the USA. Work performed in structural and glycogenomics have also resulted in the successful implementation of several technological platforms that were granted the national IBISA label. An impressive total of 61 research grants were obtained by the lab members, of which 17 from the ANR, 9 from EU PCRD programs, 1 from the NIH and several from industrial collaborations. Moreover two young PIs of the lab benefited from the very competitive French ATIP/Avenir program.

During the last period, the lab has hosted 14 postdoctoral fellows, one half being international, and 17 PhDs students have defended their thesis (17 PhDs ongoing at the time of the visit). Furthermore, at the date of the evaluation, AFMB was also hosting 24 temporary technical staff. Altogether this illustrates the outstanding capability of this lab to create and sustain a highly competitive scientific activity.

All PIs are regularly invited to international conferences and seminars abroad and in France (see teams for details). Overall, these activities confer to the lab a prominent visibility, which is also evidenced by the two scientific prizes recently awarded to lab members (1 from the French Science Academy, 1 from the International Society for Antiviral Research). From this point of view, one may also cite the exceptional visibility of the glycogenomics domain, with its leader invited to many conferences as keynote speaker.

- ## Appreciation on the management and life of the research unit

Meetings with the junior and senior staff have highlighted the very good spirit of the lab. The future project was jointly developed and all the staff adheres to it. Discussions that have led to its development have yielded new and ambitious project components. The laboratory life includes shared leadership, the regular meeting of consultation boards as well as regular scientific meetings for students. All staff are offered training activities. During the past period, the AFMB research staff consisted of three professors and three assistant professors ensuring their teaching duties, and thirteen CNRS scientists among which five were also actively participating to teaching. All teams were active in recruiting PhD students (17 theses defended between 2006 and 2010). Overall, the AFMB contributes significantly to educational activities, although glycobiology is not among the contributions provided by the lab, which is unfortunate given the local expertise. The high visibility of the lab provides AFMB with opportunities to attract PhD students. In the same way, AFMB has organized several workshops and meetings and participates actively to the animation of the campus. AFMB is therefore very structuring for the University Aix-Marseille 2, which in return strongly supports the lab and considers favorably its possible extension on the campus.

- Appreciation on the scientific strategy and the project

Thanks to its former director, the AFMB was a pioneer of structural genomics in Europe, resulting in the implementation of a technology platform, which is a leading facility for protein production in Europe. With a total of 3000 genes cloned and screened for expression since its existence (i.e. 300 genes per year on average) the RIO/IBISA platform appears a very productive and successful operation. The success of this platform for the laboratory that contributed to the Vizier European project coordinated successively by the leaders of teams 1 and 6, allowed the development of a second platform, dedicated to the screening of antiviral compounds (PCML) - gathering around 50000 compounds that was recently integrated in a larger antiviral drug design network. In parallel, the glycobiology domain of the lab gave rise to the CAZy database, which has become internationally dominant and a key resource for international collaborative projects. The implementation of cutting-edge technological resources has largely contributed to the success of the laboratory. Yet, the AFMB is now entering a post-genomic period, which required adjustments of its potential. Several personnel transfers and a careful consideration have led to restructuring the two departments in 7 teams. Following the structural genomics era, the AFMB wishes now to tackle ambitious and integrated projects in functional studies integrating molecular and structural biology, chemistry and bioinformatics.

The first theme is on molecular mechanisms of infectious diseases with a particular focus on emerging viruses. This led the AFMB to seek for local synergy by integrating the "regional Infectiopole" and participating in the project of infectious disease and microbiology Labex project. The virology department has reorganized into two teams one of which being dedicated to fundamental mechanisms in viral RNA biology while the second team will develop the medicinal chemistry component. From this viewpoint, it must be stressed that the organic chemistry group, although productive, remains of limited size, thus demanding some consideration to adapt the size and the scientific objectives. Two emerging teams in immunology and virology were created and the small team on disordered proteins was renewed. This corresponds to a wish of AFMB to diversify its projects while capitalizing on its structural expertise but it may be problematic for all teams to achieve the critical mass to match the requirements for excellence of the laboratory. Opportunities exist for some regrouping within the lab that may be considered depending on the success of these teams.

AFMB wishes also to generate a theme that develops the area of glyconeurobiology, which will be enforced by the arrival of a new PI on neurobiology, to be inserted for the moment within the glycobiology and the structural neurobiology. group. Finally, the glycobiology team, with its important CAZy database, is an original and strong team but small and needs to develop within a post-genomics environment. Linking with neurobiology is a sensible move but it may also need to consider the strengthening of functional studies in other areas. The strategy for the future of the CAZy database is to link up with INRA, which could provide the necessary technical support. Alternatives discussed are reinforcement by the CNRS. A second strategy envisioned is to exploit the in silico knowledge and start a strong research program in glycobiology.

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

Title of the team : E1 - Molecular Transport and recognition

- Team leader : Mr Christian Cambillau
- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2,5	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 engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	2
N7: Number of staff members with a HDR or a similar grade	3	2

- Appreciation on the results

The scientific activities of the team cover a broad spectrum of biological questions, from the structural biology of viruses, membrane proteins, odorant binding proteins to transcription factors and their complexes with DNA. The group works on an archaeal virus structural genomics project, which led to the structure determination of 7 proteins. The goal is to identify structural relationship of viral proteins with known protein structures and thus shed light on evolutionary relationships. A second line of interests is the structural biology of phages that can infect gram+ bacteria, a field in which the team is a world leader. The aim is to characterize structurally the phage machinery, which is employed to inject the genome. The group has determined the structures of receptor binding domain from 3 phages and analyzed their sugar binding specificities. Further structural highlights include the ~ 1 MDa large phage p2 baseplate by X-ray crystallography and EM and its activation mechanism. Another line of research concerns odorant–pheromone-binding proteins (OBP/PBP). The group has solved the crystal structure of the main antennal PBP, ASP1 in its apo form and in complex with 9-ODA. The aim is to characterize all 21 OBPs and CSPs (chemosensory proteins) of the honeybee. Along that line the group also works on OBPs from Anopheles gambiae. All these projects are of high biological relevance, and although quite diverse the quality of the research is very high. Over the last period the team has published a number of significant structural and functional insights into these biological processes.

Overall the output of the group is outstanding. The group has published 54 papers over the past period, receiving 580 citations reflecting their high impact, of which 4 PNAS, 1 EMBO J, 1 NSMB from the team (first and/or last author) and coauthored 2 Nature Methods, which represents an impressive level of productivity and place the team among the leading groups in structural virus research in Europe.

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

This team has a strong pioneering record in the development of methods for high-throughput cloning and protein production in order to obtain crystallographic structures. Thanks to its expertise, this team has participated in several EU projects as coordinator and partner, and has also attracted considerable funding during the last period to carry out its scientific projects, notably 3 EU grants, 6 ANR grants and 4 industrial contracts. The group has a large scientific network, both in France with many collaborations in Marseille, and other European countries and overseas, documented by common publications. There have also been several industrial collaborations, in particular on GPCRs and on camel antibodies. The team leader has an impressive track record and is widely considered as a world leader in the structural biology domain.

The team has attracted 3 post-docs, 2 of which are international, and 6 PhDs students who defended their thesis during the last period and 3 are still ongoing. The group relies heavily on temporary staff, which while highlighting its success for attracting financial support represents a potential threat for the future. It is particularly important to note that the team leader, who will retire at the end of the coming period, proposes to gradually move out to a potential successor.

- Appreciation on the scientific strategy and the project

Since the team leader and another senior scientist will leave at the end of the next evaluation term, most of the future projects concern a continuation and extension of the current program. This is reasonable and will provide time to finish some of the interesting research projects. The team proposes to extend its interest to the type 6 secretion system of bacteria. The future focus on bacterial secretion systems is competitive and ensures international visibility. It includes cutting edge technology and further development of this technology. The overall strategy towards the end of the next period is to focus on the most successful projects. Funding has been currently secured until 2013 and 1 supplementary ANR grant was recently submitted.

- Conclusion :

— Summary

This team has made excellent contributions to structural biology, and presently enjoys high visibility amongst its peers. The group is highly productive, and is among the leading groups in structural virology in Europe. The structural genomics technologies have enabled the team not only to become a major player in structural genomics in Europe, but also to tackle difficult exciting biological problems where the production of proteins and of large protein complexes is often the most challenging part of the project. The past, current and future research program is solid and exciting science that targets a number of different problems in biology with a major focus on viruses/phages. The current proposal for the next 4 years is feasible and in line with the expertise of the team.

— Strengths and opportunities

- Strong and foresighted leadership of the team leader.
- Excellent infrastructures developed by the pioneering work of the team.
- A proven record of success in terms of securing funding, attracting international scientist to the lab and producing high quality research papers.
- Integrated projects on the basis of exciting structural results.
- Anticipation of a shift in the leadership from the team leader to a younger PI.

— Weaknesses and threats

- No major weakness has been identified.
- A threat lies in the fact that the change in leadership can affect the productivity of the team.
- The potential (proposed) new team leader has still to develop its own research program.

— Recommendations

- The transition period has to be carefully planned.

- The high visibility of the AFMB might be exploited to attract an internationally recognized structural biologist to succeed the current team leader.

Title of the team : E2 - Structural Glycobiology and Neurobiology

- team leader: Mr Yves Bourne
- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	3
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	1
N7: Number of staff members with a HDR or a similar grade	2	4

- Appreciation on the results

The main research activities of the team are in the area of structural neurobiology and glycobiology. The scientific questions addressed in the glycobiology area are in particular the molecular structure and the function of a number of enzymes involved in the biosynthesis and processing of glycoconjugates. The latter play a significant role in many biological processes. During the last four years, the team has solved a number of novel structures of glycoside hydrolases, glycosyltransferases and the likes, often as complexes with substrate and/or products, which increases the mechanistic insights from these studies. A second research focus of the team is structural neurobiology, where a number of excellent new findings have been obtained concerning the function of acetylcholinesterases, and proteins and protein complexes that are components of synapse formation and maturation.

Since 2006 the team has published 35 peer-reviewed articles, in internationally peer-reviewed journals of which 22 from the team (first and/or last author: 3 EMBO J, 1 PNAS and 1 Nature Biotechnology) and important co-author papers (e.g. 1 Neuron), indicating an excellent productivity. Outstanding contributions are the structure determination of a neurexin/neuroligin complex and delineation of the structural determinants for high affinity binding in the acetylcholine binding protein and its interactions with a neuronal acetylcholine receptor.

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

The team is involved in a number of national and international collaborations, including an industrial partner, and several of these have led to excellent publications, indicating that these collaborations are very successful. The team led by Dr. Bourne has been a partner in the FP6 EU project SPINE 2 and has also attracted

9 other research contracts from other various sources including 3 from ANR. 3 PhDs defended their thesis during the period and the team has attracted 4 postdocs. The team has thus shown a strong attractiveness, as also evidenced by the number of collaborations in Europe and in the US.

- Appreciation on the scientific strategy and the project

The proposed activities of the research team are well conceived and built on the leading role in structural neurobiology and glycobiology. A future strength of the team will be the emphasis on neuroglycobiology with the arrival of a new team member working on a topic, which is a strong and important new activity with a great potential. The arrival of P. Marchot will also strengthen the pharmacology aspects of the neurobiology projects. For the next period the team wants to focus and further develop their very successful research projects in these areas. A strong collaboration with team 3 in the area of glycobiology will be continued which in view of the leading role of this group most certainly will lead to significant and novel discoveries in this field. The scientific questions pursued by the team are not only highly relevant for new biological/biochemical insights, but also of great interest from a medical perspective. The neurobiology work has potential implications for neurological diseases such as Alzheimer, and the project on bacterial pathogenicity is very appropriate in view of the alarming increase in antibiotic resistance.

- Conclusion :

— Summary

- The group has made excellent contributions to structural biology, and enjoys a high international reputation. The group is very productive and competitive; the work carried out over the years has placed the team among the leading groups in structural neurobiology.

— Strengths and opportunities

- Strong leadership.
- Multidisciplinary approach and integrated approach to structural glycobiology, with a variety of methods available in-house.
- Arrival of neuropharmacologist in the team with a very strong record who will give the team a strong basis to maintain and further develop their competitiveness also into the future.

— Weaknesses and threats

- A somewhat too wide range of subjects and, in view of the limited size of the group, a risk of too much diversity that could potentially spread the resources too much.

— Recommendations

- Make sure that each project has appropriate human resources, in particular by ensuring the presence of doctoral students working on each project. Presence of more PhDs in the team will also improve the team involvement in student training.
- Try to get involved in teaching to allow students to benefit from a strong expertise and to increase visibility for potential PhDs.

Title of the team : E3 - Glycogenomics

- Team leader : Mr Bernard Henrissat
- Staff members

	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)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	1
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

The research activity of the team is focused on glycogenomics. This team is responsible for a unique and distinctive activity that has clear global leadership. Based on excellent expertise, they developed an in silico pipeline allowing the efficient prediction and annotation of the so-called CAZymes which encompasses glycoside hydrolases, glycosyltransferases, polysaccharide lyases, carbohydrate esterases and carbohydrate-binding modules. The strategy is based on a precise subfamily definition that proved to be the unique efficient way to lower errors and mis-predictions. This small research team has not only made an exceptional impact on the field, but it has been also instrumental and central in pioneering, establishing and developing the field of glycogenomics. This team is highly focused and continues to make a significant impact in a clear and defined area of activity in terms of both its online glycogenomics resource and associated publications.

The underpinning research has been sustained throughout the 2006-2010 period with considerable impact in terms of both publications in leading international journals and also the widely used, world-leading online resource of CAZy.org. For such a small team of only 2 scientists the output in terms of publications is truly impressive with contributions to 61 papers in the world's leading journals and over 12 in Nature, Science and PNAS alone. The team paper describing the CAZy database in NAR in 2009 is the most cited French paper of 2009 in the Biochemistry and Molecular Biology (source: ISI Web of Knowledge).

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

The in silico tools developed are internationally recognized as leading the field and allowed them to participate to numerous world-wide genome sequencing projects with the specific objective of annotation of the CAZYmes. The team is exceptionally strong in terms of its international profile and reputation and shows strong participation in networks at national and international levels. The team members have participated in several stable long-term networks. The team is responsible for a highly visible activity and very influential at the global level. The team has been invited in an impressive number of meetings, of which 14 international conferences (4 Gordon conferences).

In addition to the 2 permanent scientists, the current staff is composed of 1 PhD student and 1 post-doc. During the 2006-2010 period 3 post-doc and 1 PhD were present, thus emphasizing a potential attractiveness of the team although welcoming young scientist remains a shortcoming of the team.

The team has successfully applied for competitive funding; It currently has 7 grants among which 1 FP7 program and 2 ANR.

- Appreciation on the scientific strategy and the project

The long-term project is clearly feasible and focuses on the development of a more efficient in silico database and annotation pipeline to cope with the growing amount of sequence data. Some optional projects are linked to the expansion of the team. These could build on annotation of metagenomes, the increased exploitation of the accumulated knowledge for industrial application (blood group interconversion, xeno-transplantation…) and also allow the team to play an active role in the emerging field of system glycobiology. Along these lines, funding has been currently secured until 2012 via 1 FP7 grant. The project for the continuation of the in silico research program is in place but will have to deal with large increases in data and how this is envisioned is not clear as cutting edge technologies and diversifying projects are mostly envisioned in the framework of the optional projects. The team is of the highest excellence but, as it is only two members, it is vulnerable to change and does not have critical mass to maintain creativity. In the immediate coming years, the team is likely to maintain international relevance and excellence but additional resources will be required to stabilize the activity and to deal with changes in the field. The next few years will see an increase in the number of genomes and the team needs to be positioned to maintain dominance and to adapt to allow innovation in a post-genomic environment.

- Conclusion :

— Summary

This is a world-leading team performing an outstanding activity well ahead of the competition. It needs to capitalize on this in next phase of glycogenomic information curation and also to exploit discovery potential of the CAZy resource. Less than 5% of CAZy sequences have a defined function and there is much potential to expand in this area of functional analyses and applications which have not been followed up to-date due to the small size of the team.

— Strengths and opportunities

- Great leadership of the team leader and complementarities of expertise within the team.
- Massive intellectual property potential of the CAZy resource.
- Interest showed by INRA that can help raising appropriate human resources.
- Strong possibilities of interactions with industry.
- Increased integrated activity with Structural Glycobiology as both teams move into areas of metagenomics and micobiomes.

— Weaknesses and threats

- Discovery potential of the resource has not been maximized by the team due to lack of manpower.
- The small size of the team is a major worry.
- Funding sources not clear.
- Competition likely to increase in near future.

— Recommendations

- The team must look at ways to expand core staff to be prepared for post-genomics system glycobiology.
- The means to move toward functional studies are still unclear and should be thought trough.
- A clear strategy for the future of the CAZy database needs to be defined.

Title of the team : E4 - Structural Immunology

- Team leader : Mr Alain ROUSSEL
- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
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)	0	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 engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	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	2	3

- Appreciation on the results

This team is headed by a DR2 CNRS and includes a second DR2 CNRS, 1 CR1 CNRS, 1 IR2 CNRS and 1 temporary technical staff. This team comes from the merging in January 2010 of the following two groups: the « Structural NMR » team from AFMB and the "Structural Immunity" team who left the Centre de Biophysique Moléculaire in Orléans and joined the AFMB in January 2010. This last group was created in 2005 and benefited from an ATIP CNRS program for the 2006-2008 extended up to 2010. This restructuring corresponds to the implementation of former recommendation of fostering a clear scientific strategy for the NMR team. A refocusing of the scientific topics tackled by the NMR group on subjects brought by the immunology group is expected.

The NMR group has developed three research projects covering: i) the structure of peptidic blockers of ion channels; ii) the properties of unfolded viral proteins and iii) the structure of proteins involved in a secretion system of Pseudomonas aeruginosa. In the two latter, the group acted as the structural partner for external projects. Regarding the Immunology group, the projects focused on the structural biology of the cell actors involved in the activating cascade of the TOLL receptor during the innate immune response to Drosophila infection by gram- and gram+ bacteria. Several structures were solved including the structure of PGRP-SD, a peptidoglycan recognition protein, of the GNBPlike-3 protein and that of the serine protease Grass, which represent the first structure of a clip-domain serine protease. Since its arrival in Marseille, the group has also reported the structure of two domains of the peptidoglycan-recognition protein LF (PGRP-LF), a negative regulator of the Immune deficiency pathway (IMD) in drosophila and they also expressed and purified the N-terminal domains of ModSP, a protease involved in the Toll activation cascade.

During the previous period both partners have published respectively 13 and 11 papers in peer-reviewed journals, of which 7 (1 J. Mol. Recog., 1 J. Struct. Biol., 1 Protein Sci.) and 5 (1 Mol. Immunol., 2 Acta Crystallogr., 1 JBC) originating from the groups own projects and 1 Embo J. as co-author in 2006. This represents a little limited productivity. However, one may note a recent take-off of the research themes initiated at the CBM that triggered an increase in the number and quality of the papers.

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

The structural NMR team interacted significantly with other teams of the AFMB in particular the structural disorder team with which a project on the measles virus was very productive. Thanks to its leader being recognized as an expert in the toxicology field, the NMR group benefits from a fair visibility and has thereby a good capacity to attract students with 6 on-going or recently defended thesis and several well established collaborations. Yet these are mainly local or national. The fact that the team activity was so far driven by its expertise rather than by their own project resulted in a limited capability of self-financing with two participations in ANR grant as partners, of which one from another group of the AFMB. On the other hand, the immunology group was founded by an ATIP grant and was the recipient of 8 grants, of which 2 ANR and will benefit from two other ANR grants for the coming years (ANR MIME for the period 2008-2011; the team also participates in a non thematic ANR for the period 2010-2012).

Both partner groups showed limited international presence with 4 participations of senior scientists to international meetings, one as an invited speaker.

- Appreciation on the scientific strategy and the project

The integrated team proposes five research themes. The main project is the continuation of the encouraging results obtained by the immunology group on the structures of the proteins involved in the Toll activation. The team intends in particular to determine the X-ray structure of the ModSP serine protease and to identify the partners of its 6 N-terminal domains. A second project that will be undertaken by the NMR subgroup concerns the deciphering of the structures and interactions between several protein domains involved in the immune deficiency pathway in particular deriving from Imd, PGRP-LC and the FADD. The third project is dedicated to a thymus protease involved in the maturation of B lymphocytes. The fourth project concerns the CD36, a membrane glycoprotein family involved in immunity, the crystallization of which will be attempted. The role in phagocytosis of two CD36 representatives will be further studied in drosophila cell system. Finally, the last project is the continuation of the historical toxin thematic aiming to understand the interaction of peptidic blockers of ion channels with their targets by deciphering the mechanism of action responsible for the blocking of the RRY calcium receptor by the Maurocalcin (MCa) toxin.

- Conclusion :

— Summary

This team originated in the merging of two structural biology groups. The first group has a recognized but unfocused expertise in NMR and peptide structures whereas the second group provides a solid expertise in the structural biology of the proteins involved in the innate immune response. The recent productivity was somewhat limited and a synergy is expected from this restructuration. There are various projects capitalizing on the expertise of drosophila immunity, a new field of investigation for AFMB which therefore presents some risks of a thematic dispersal.

— Strengths and opportunities

- The excellent expertise of the team members in structural biology.
- The presence within the team of two senior scientists, respectively expert in drosophila expression system and leader of the AFMB protein production platform for X-ray studies.

— Weaknesses and threats

- Owing to restructuring, the NMR will be torn between the new immunology projects, which represent a serious workload, its historical themes and the productive collaboration with the Structural Disorder team, which might suffer from this new positioning.
- A low productivity in the past period.
- Many projects, with high workload, one of which (the CD36 project) being not well grounded in the expertise of the team as it involves a lot of cell biology and expertise with membrane proteins.

- The lack of financing for most projects other than the TSSP side-project.

— Recommendations

- It will be important for this team to carefully reconsider its overall project to define objectives that are better suited to the AFMB environment in order to capitalize on the synergy that are to be found with other teams. This will facilitate attracting the appropriate financial support.
- Seek collaborations with the Centre d'Immunologie de Marseille-Luminy (CIML).

Title of the team : E5 – Viral enzymes : Structure and Mechanisms

- Team leader : Mr Bruno Canard
- Staff members

	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	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	5	3
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	4	4

- Appreciation on the results

This team headed by a DR1 CNRS includes 1 CR1 CNRS, 1 PR, 1 CR2, 2 MCFs, 1 IR2 and 1 IE. During the last period, the team had two more senior scientists (1 CR1, 1 CR2) and 1 IE, who have departed to participate to another AFMB team following the restructuring of the unit.

Under the leaderships first of the historical leader of the lab and then this team leader, AFMB has developed and operates an integrated structural genomics platform. This platform allowed this team to promote and participate to the collaborative VIZIER European project, dedicated to structural virology with a special emphasis on novel or emerging infectious agents. Since the beginning of the project, this project resulted in 39 deposits into the PDB, among which the seminal crystal structure of the West-Nile virus polymerase, the SARS-CoV nsp9, nsp15 proteins and the nsp10/nsp16 capping complex, and the N-terminal domain of the L-protein of the LCMV. In terms of mechanism of action, these successes led the team to pay a special attention to the RNA capping machinery of flavivirus and coronavirus, a topic that will form one of the two research themes for the next period.

Over the 2006-2010 period, the team was organized in subgroups, one of which was formed around two young chemist PIs whose activity was devoted to medicinal chemistry with the aim to develop novel antivirals. Promising results were obtained for thiophoshonates derivatives against HIV reverse transcriptase and with phosphoramidate dinucleotide directed against HCV NS5B polymerase. Taking advantage of a collaborative network established with local laboratoires devoted respectively to drug screening and viral strains archiving,

the team also operates an antiviral drug design platform (AD2P), which has undertaken projects on other pathogens such as Dengue virus.

The expertise of the team and its European influence are reflected by its very strong contribution to the structural virology domain. The productivity of this team over the last four years has been excellent with a scientific contribution amounting to 73 articles, of which 39 originating from the team (First and/or last author) in top-ranked peer-reviewed journals (EMBO J, PNAS, NAR, J Mol Biol, PloS Path).

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

The team hosted 14 foreign invited scientists from all over the world for short exchange periods. The team leader was awarded an international prize from the International Society for antiviral research. The team was granted 17 research contracts from various sources (among which 2 ANR MIME, 1 non thematic ANR, 2 FP6 projects and 1 FP7 RI). The main characteristic of this group is its remarkable insertion within international networks. Thanks to VIZIER and the current EVA European program, this team contributes efficiently to the Structural Virology domain at the European level. 5 students defended their PhD over the period and two theses are ongoing. Two patents were filed in the medicinal chemistry domain. A young scientist was recently hired as CR2 CNRS reinforcing the team.

- Appreciation on the scientific strategy and the project

After a very productive period orientated toward the solving of many structures of viral proteins within the framework of the VIZIER program, the project of the teams corresponds to a refocusing on fundamental virology with two complementary research topics. 1/ Structural and functional studies of viral RNA capping and 2/Structural and functional studies of RNA synthesis, with a particular attention paid to such health threats as flavirivirus, alphavirus, coronavirus, arenavirus and picornavirus. Financing of these activities is already guaranteed as the team has already obtained one FP7 IP, is part of an FP7 Marie-Curie Network and participates to the European Virus Archive initiative.

- Conclusion :

— Summary

This is an internationally renowned team led by a charismatic young leader. Thanks to the European network that the team contributed to create, it is at the heart of the European infrastructures for structural virology. Owing to its tight collaboration with local team devoted to the identification and preservation of new or emerging viral strains (SARS, chickungunya) the strategy of this group was so far to focus on obtaining original structures and deriving information for designing novel antivirals. In return, despite some insights on flavivirus and coronavirus RNA capping mechanism, the team did not devote much workload to deciphering fundamental mechanisms. Refocusing its activity might therefore allow the team to play a forefront role in fundamental virology studies.

— Strengths and opportunities

- Team perfectly positioned at the heart of European virology project with a solid collaborative network and benefiting from both structural genomic and drug-screening platforms.
- Several experienced PIs with young researchers.
- An outstanding capacity to obtain financial support for the project, resulting in strong attractiveness.

— Weaknesses and threats

- A decision to develop EM macromolecular complexes studies which will require technical staff and expertise.
- A refocusing on fundamental viral mechanisms which will require defining high-profile integrated projects with the appropriate mass of ressouces devoted to it, to impact significantly a very competitive field.

— Recommendations

- Maintain a tight collaboration with the medicinal chemistry group, (team 7), the activity of which remains very close to that of this team.
- Develop more collaboration with cellular virologists to develop integrated project from structural to cellular virology.

Title of the team : E6 – Structural disorder and molecular recognition

- Team leader : Ms Sonia LONGHI
- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
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	
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	3
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

This small team is independent since 2006. The focus of the work is on the characterization of intrinsically disordered sequences present in proteins regulating the replication machinery of measles virus, a member of the paramyxoviridae. The merit of this team lies in its commitment to sensitize the field of paramyxovirus replication for the functional role of disordered regions in P and nucleoproteins as it was one of the first team to tackle this problem. This type of research is very important and has contributed to the understanding of the replication machinery of negative strand RNA viruses. In the last four years the team has focused on the specific interaction of Ntail with P, hsp70 and IRF-3p partners by using mutagenesis, CD and EPR to map the residues relevant for induced folding. Subsequent NMR analyses revealed the transient alpha-helical conformation of Ntail and highlighted the formation of an “encounter complex” that was further confirmed by EPR. In parallel of, a meta-server was developed to predict intrinsic protein disorder.

Overall, the team has published 26 papers over the past period, of which 8 publications originated from the team (first or last author) (1 J. Phys. Chem, 1 J. Mol. Recog., 1 BMC Genomics) , 10 as a co-author and 8 review articles. The productivity and quality of paper is therefore good with regard to the small size of the team although no papers in high or medium impact factor journals were recorded.

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

This team maintains a good international visibility evidenced by the 7 international invited conferences, among which 2 Gordon Research conferences. Nevertheless, the team is not very active in attracting young scientists with one post-doc recruited during the last period and one PhD ongoing (no defense since 2006). The team has thus relied on temporary technical staff hired thanks to its successfully application for competitive funding; it had 1 ANR grant and partnered an NIH grant. It currently has 2 active ANR grants, one of which as coordinator. Several national and international collaborations are developed with common publications.

- Appreciation on the scientific strategy and the project

The projects are mostly the continuation and extension of the past with new collaborations. Funding has been currently secured until 2013 via 1 ANR grant, warranting the feasibility of the program. Yet, the continuation of the research program lacks some originality with the cutting edge technology required for the program mostly applied via collaborations.

- Conclusion :

— Summary

The past, current and future research program is sound science that targets the function of disordered protein regions in negative strand RNA virus replication processes. The record of the PI will ensure results in the future.

— Strengths and opportunities

- Experience of the PI to work with disordered proteins.
- Opportunity to develop single molecule techniques to study the replication process.

— Weaknesses and threats

- The program does not go beyond the description of interactions of disordered protein regions, thus lacking a strong integration of these results into the biological context.
- Most of the future research depends on collaborations with groups with expertise in EPR, NMR or crystallography.
- The group does not have its own expertise in cutting technology required to study intrinsically disordered proteins within a highly competetive international environment.
- Small size of the group.

— Recommendations

The research is carried out within a network of collaborations thanks to which the team gains access to state-of-the art technologies. However, it would be advisable that the PI takes on the lead role in the projects to avoid being too dependent on external teams. Attracting young scientist and maintain strong internal interactions would be a good way to reinforce the potential of the team.

Title of the team : E7 – Medicinal chemistry and Structural biology

- Team leader : Mr Julien LESCAR
- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	1
N7: Number of staff members with a HDR or a similar grade	1	2

- Appreciation on the results

The « Medicinal chemistry and structural virology » group is a new team resulting from the merging of the previous "proteins from emergent viruses team and parasitology" and the medicinal chemistry group headed by PI who was participating to the former virology department. The main activity of the group concerns structural studies of emerging RNA viruses, covering flaviviruses, coronaviruses and bunyaviruses. Key results were the structure of the West-nile virus RNA dependent RNA polymerase, in collaboration with the molecular virology team, and the first detailed structures of the NS3 helicase in complex with RNA and nucleotides, published in EMBO J. During the 2006-2010 period, the group was divided between Singapore where the team leader led a structural biology group and Marseille, with many collaborations on both sites (notably the Novartis Institute for Tropical Diseases at Singapore, Over the 2006-2010 period, the group has produced 30 publications in international peer-reviewed journals, of which 18 from the team (first and/or last author, 1 EMBO J, 3 J. Virol, 1 Curr Opin Struct Biol), representing a very good productivity for this small team (although it is difficult to set the different contributions apart due to the restructuration of the teams).

- 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 joined AFMB in 2007 with the support of an ATIP program 2008-2010. The international visibility of the team is promising, due to the close partnership developed with labs in Singapore (Novartis Institute for Tropical Diseases, Institute of Molecular and Cell Biology, Nanyang Technological University). The financial support of the team was provided by an ATIP grant that started from 2008 and various financial support in Singapore. The team leader has supervised 4 PhDs and 6 postdoctoral fellows during the last period. He has established fruitful collaborations with US and Australian groups in the field of flaviviruses and Bunyaviruses and was invited to 3 international meetings.

- Appreciation on the scientific strategy and the project

The project will be situated at the interface between structural biology and medicinal chemistry. Three research themes are foreseen: Theme 1 concerns the structural virology of Bunyaviridae, with structural and

functional studies of a RNA packaging protein. This theme also involves a collaboration with the screening platform AD2P The search for compounds able to interfere with multimerization of the N protein or RNA binding is also planed. Theme 2 concerns structural biology of Flavoviridae and drug design, targeting NS5 polymerases and RNA unwinding by the NS3 RNA helicase. This theme involves a drug discovery approach using fragment libraries, with the use of biophysical methods to identify small fragments that bind to NS3 helicase domain, hit to lead optimization of already identified compounds targeting the NS5 polymerase of the dengue virus, and the NS5B polymerase from HCV. The third theme concerns the drug-design and development of nucleotides analogues active against HIV and HBV infections. A last project concerns structural studies of enzymes from plasmodium falciparum, a project started recently by this team.

- Conclusion :

— Summary

This new team results from the return to AFMB of a young scientist, previously assistant professor at Singapore University, who develops an activity based on a strong expertise in structural virology notably on several emerging viruses, with a recent focus on medicinal chemistry, taking advantage of the arrival in this team of two organic chemists among whom an experimented young PI. The team is well funded, with an ATIP program (2008-2010), a PICS with Singapore, and the European Integrated project "SILVER". Strong collaborations exist with the molecular virology team and maintain a tight link with the Singapore University for complementary approaches. It is not clear whether the size of the medicinal chemistry group is likely to evolve or if it will remain as such. In the latter case, it will be probably too limited for the tasks proposed.

— Strengths and opportunities

- Multidisciplinary approach well suited for antiviral drug development.
- Association both with the EU SILVER project and the AD2P platform.
- A strong network of collaborations both within AFMB and at international level due to the past experience of the PI in Singapore.
- An experienced young leader.

— Weaknesses and threats

- Integration of chemistry and structural virology groups not yet evident.
- Chemistry resources too limited for the number of targets.
- Topics sharing between this team and the molecular virology not well defined.

— Recommendations

- Reinforce medicinal chemistry and collaborations with external pharmacologists in order to be actually capable of impacting the antiviral field.

Notation

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
AFMB - ARCHITECTURE ET FONCTION DES MACROMOLÉCULES BIOLOGIQUES	A+	A+	A+	A	A+
STRUCTURAL GLYCOBIOLOGY AND NEUROBIOLOGY [BOURNE-BOURNE]	*A+*	*A*	*Non noté*	*A+*	*A+*
MOLECULAR TRANSPORT AND RECOGNITION [BOURNE-CAMBILLAU]	*A+*	*A+*	*Non noté*	*A+*	*A+*
VIRAL ENZYMES: STRUCTURE AND MECHANISMS [BOURNE-CANARD]	*A+*	*A+*	*Non noté*	*A+*	*A+*
GLYCOGENOMICS [BOURNE-HENRISSAT]	*A+*	*A+*	*Non noté*	*A*	*A+*
MEDICINAL CHEMISTRY AND STRUCTURAL BIOLOGY [BOURNE-LESCAR]	*A*	*A*	*Non noté*	*A*	*A*
STRUCTURAL DISORDER AND MOLECULAR RECOGNITION [BOURNE-LONGHI]	*A*	*A*	*Non noté*	*B*	*A*
STRUCTURAL IMMUNOLOGY [BOURNE-ROUSSEL]	*A*	*A*	*Non noté*	*B*	*A*

C1 - Qualité scientifique et production
C2 - Rayonnement et attractivité, intégration dans l'environnement
C3 - Gouvernance et vie du laboratoire
C4 - Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)*

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	42	5	20	26	36	59	5	17	29	239
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

* les résultats SVE2 ne sont pas définitifs au 06/05/2011

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

- SVE1 Biologie, santé
  - **SVE1_LS1** - Biologie moléculaire, Biologie structurale, Biochimie
  - **SVE1_LS2** - Génétique, Génomique, Bioinformatique, Biologie des systèmes
  - **SVE1_LS3** - Biologie cellulaire, Biologie du développement animal
  - **SVE1_LS4** - Physiologie, Physiopathologie, Endocrinologie
  - **SVE1_LS5** - Neurosciences
  - **SVE1_LS6** - Immunologie, Infectiologie
- SVE2 Ecologie, environnement
  - **SVE1_LS7** - Recherche clinique, Santé publique
  - **SVE2_LS8** - Evolution, Ecologie, Biologie de l'environnement
  - **SVE2_LS9** - Sciences et technologies du vivant, Biotechnologie

UNIVERSITÉ DE LA MÉDITERRANÉE
AIX-MARSEILLE II

Objet : Réponse au rapport d'évaluation - **S2UR120001630 - AFMB - Architecture et Fonction des Macromolécules Biologiques - 0131843H** - de l'unité AFMB - Architecture et Fonction des Macromolécules Biologiques

Observations d'Aix-Marseille Université

Comments concerning the overall appreciation of the laboratory

The redistribution of the smallest teams which might be not optimal, had been largely discussed during the preparation phase of the evaluation process, and the reflection on this matter will be pursued. As well, the position of organic chemistry within projects may appear somehow weak, and the unit will also address this concern carefully.
The emergence of a new team to develop new topics in the field of Structural Immunology had been decided in agreement with the scientific objectives and research directions of the laboratory and in view of the departure of prominent scientists, and clearly not as a "*risk of thematic dispersal*".
Electron microscopy has been implemented at the laboratory level, not only the virology team, to enlarge the range of complementary techniques in structural biology available in-house, and expertise in this field is already present within the permanent staff.
The future of the NMR technique is currently being discussed to better delineate its contribution to the research projects of the lab.

Comments concerning the evaluation of team E1 – C Cambillau

The forthcoming retirement of the present group leader may lead to a loss of expertise, subjects and scientific production for the group. However we concurred on that the change in leadership has to correlate with the gradual emergence of a new leader with appealing subjects and substantial funding. This strategy is expected to lead to a consensual transition before the end of the next period. It is by no means incompatible with the idea of attracting other internationally recognised structural biologists to the AFMB to install and develop their own teams and research, an idea that, would have a positive impact in the laboratory.

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Comments concerning the evaluation of team E3 – B Henrissat

The weaknesses of the team have been clearly identified, in particular the need of additional staff members to maintain our leadership, to embark on new challenges and to better exploit intellectual property. We fully share this analysis. The success of the CAZy database is mainly due to the fact that we have been able to carry the underlying research on a long duration, made possible by a peculiarity of French research: permanent staff. Indeed, short term ANR/EU funds are inappropriate for long term database developments and services. Instead we believe that CNRS and Universities can play a major role, by providing the appropriate human resources. A bioinformatician, trained in the best US institutions, is currently applying to a Chargé de Recherche (CR1) position in CNRS sections 21 and 22. We have also identified suitable IR2-level engineer candidates, some with extensive experience gained at the European Bioinformatics Institute. Because of the large volume of work performed in collaboration with this institution, we have also initiated discussions to establish a contractual relationship with INRA.

Comments concerning the evaluation of team E4 – A Roussel

We would like to address some clarifications on the following points:

« Owing to restructuring, the NMR will be torn between the new immunology projects, which represent a serious workload, its historical themes and the productive collaboration with the Structural Disorder team, which might suffer from this new positioning »
The only person involved in NMR (H Darbon) is also the responsible of the master BBSG and has a full time teaching duty (128 hours/year). The Imd pathway project will become his main subject. His future involvement in his historical toxinology project and in the in-house collaborative studies on disordered proteins will remain occasional.

« Many projects, with high workload, one of which (the CD36 project) being not well grounded in the expertise of the team as it involves a lot of cell biology and expertise with membrane proteins »
The aim of the CD36 project is to solve the crystal structure of the soluble ectodomain, not the entire membrane protein. At the AFMB we are setting up new cell biology tools to expand the portfolio of techniques and to conduct integrated projects in the laboratory.

« The presence within the team of two senior scientists, respectively expert in drosophila expression system and leader of the AFMB protein production platform for X-ray studies »
We greatly appreciate the presence of the leader of the protein production platform in the team, consciously of his primary engagements on projects devoted to the IBISA structural genomics facility.

« It will be important for this team to carefully reconsider its overall project »
As already discussed during the oral presentation, the number of projects of the team will be decreased to be in accordance with the manpower of the group.

Comments concerning the evaluation of team E6 – S Longhi

We would like to clarify the following points.

"The productivity and quality of paper is therefore good with regard to the small size of the team although no papers in high or medium impact factor journals were recorded."
Although the team has not published in journals with IF > 5, the published papers over the 2006-2010 period gave rise to a total of 466 citations (h index = 11).

"Nevertheless, the team is not very active in attracting young scientists with one post-doc recruited during the last period and one PhD ongoing (no defense since 2006)."
Although no PhD thesis has been defended since 2006, the team was able to attract two foreign students who were successful in the highly competitive Erasmus and Extra applications. In addition, the team was successful in the application to the Vinci program for a PhD fellowship granted by the franco-italian university (in 2010 only 3 such PhD grants were available for the entire France and for all disciplines), and was also provided a PhD fellowship by the CNRS and the DGA. When the AERES committee visited the lab, the PI was already supervising three PhD students (and not one), which is the maximum number of students that can be supervised.

"The projects are mostly the continuation and extension of the past with new collaborations."
The project has been thoughtfully built so as to be adequate to actual human resources and to avoid thematic dispersion. Nevertheless, the project implies at least three new sub-topics.

Weaknesses and threats

"The program does not go beyond the description of interactions of disordered protein regions, thus lacking a strong integration of these results into the biological context."
As indicated in both the Report and the Project, the functional impact of N_{TAIL} and P_{XD} substitutions has been and will be assessed in vivo in the context of measles virus infection (collaboration with D. Gerlier, Lab. Virologie Humaine, Lyon and with M. Oglesbee, Ohio State University), as already successfully achieved in the past (see Zhang et al. Virology 2005)

"Most of the future research depends on collaborations with groups with expertise in EPR, NMR or crystallography.
The characterization of IDPs does not rely on a single technological expertise. Thanks to its expertise in the field of IDPs, the PI has been able to federate collaborators with different biophysical expertise to tackle a biological question that is being paid an increasing interest and that the PI greatly contribute to develop. This wide collaboration network is more an opportunity than a threat.

Comments concerning the evaluation of team E7 – J Lescar

We would like to address some comments and concerns raised by the AERES committee.

« It is not clear whether the size of the medicinal chemistry group is likely to evolve or if it will remain as such. In the latter case, it will be probably too limited for the tasks proposed »

The medicinal chemistry group will grow as a normal and expected progression. The work force is composed by two permanent organic chemists including an experimented young PI who has established fruitfull collaborations with organic chemists from the « National Library network ». Please refer to the list of chemist collaborators below. The number of the projects and the advance will be in accordance with the available manpower.

Weaknesses and threats

- *Integration of chemistry and structural virology groups not yet evident.*
- *Chemistry resources too limited for the number of targets.*
- *Topics sharing between this team and the molecular virology not well defined.*

Recommendations - Reinforce medicinal chemistry and collaborations with external pharmacologists in order to be actually capable of impacting the antiviral field.

The idea to bring together « chemistry » and « structural virology » is supported by the need of both disciplines in nearly every projects developed in the team. Antiviral development by rational design or screening strategies requires structural data to understand hit/target interactions and to synthesize improved molecules. Structural virology also makes extensive use of molecular probes that are available through organic chemistry. The number of medicinal chemistry projects will be in adequacy with the work force. To be able to perform projects with middle-throughput synthesis « hit to lead optimisation », the chemistry lab is equiped with parallel synthesis and purification facilities. Well-established collaborations are currently on-going with the following chemists: J Vasseur (IBMM, Montpellier), Pierre Vierling (Molécules Bioactives, Sofia Antipolis, Nice), Chimiothèque Nationale: M. Hibert (UMR 7200, Illkirch), F. Gueritte (ICSN, Gif-Sur-Yvette), F. Mahuteau (Institut Curie, Orsay) and pharmacologists (JL Galzi, « Preclinical Drug technology », Illkirch). As recommended by the AERES committee, we will seek further collaborations in the coming months.

En accord avec les deux autres établissements d'Aix-Marseille

Le Président
de l'Université de la Méditerranée

Yvon BERLAND

Le Vice-président du Conseil Scientifique
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