Intéractions et modulateurs de réponses

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

UPR 3243 - Interactions et Modulateurs de Réponses

From the

CNRS

January 2011

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

Section des Unités de recherche

AERES report on the research unit

UPR 3243 - Interactions et Modulateurs de Réponses

From the

CNRS

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: Interactions et Modulateurs de Réponses

Requested label: UPR

N° in the case of renewal: 3243

Name of the director: Ms Françoise GUERLESQUIN

Members of the review committee

Committee chairman

M. Jean-François MOUSCADET, ENS Cachan, France

Other committee members:

Ms Claudina RODRIGUES-POUSADA, New University of Lisbon, Portugal

M. Alexandre BONVIN, Utrecht University, the Netherlands

M. Patrick TAUC, CNRS, CoCNRS

M. Bruno VILLOUTREIX, Université Paris-Diderot, France

M. Winfried WEISSENHORN, Université Joseph Fourier, Grenoble, France

Observers

AERES scientific advisor

M. Yves GAUDIN

University, School and Research Organization representatives

M. Jacques MARVALDI, directeur de l'UFR SVTE, Université de Provence

M. Gilbert DELEAGE, INSB, CNRS

M. Younis HERMES, Délégué Régional CNRS

Report

1 • Introduction

- **Date and execution of the visit**

The visit took place on January 26th, 2011. An international team of 6 scientists, with expertise in the research areas of the 3 teams associated within the IMR, conducted it. The visit started with a general presentation of the history of IMR by the head of the lab, its past and future organization, and its main achievements and projects. The three team leaders presented their results and projects and answered to questions of the committee members. The latter met successively the students and postdocs, the technical staffs and the staff scientists. The committee questioned the CNRS and University Aix-Marseille I representatives about the place given to the laboratory in their respective scientific policy as well as its importance in the regional and national context. Finally, the committee questioned the lab head during a closed-door meeting that was followed by the final deliberation of the committee and the preparation of the present report.

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

The laboratory "Interactions et modulateurs de réponse" (IMR), UPR3243 CNRS, is located on the CNRS Campus Joseph Aiguier, in Marseille, where it occupies 504 m2 in renovated facilities. The lab was created in 2008 by two teams that chose to split from the UPR 9036 to start a new research unit dedicated to deciphering the molecular basis of protein/protein interaction by means of NMR and bioinformatics and to apply this knowledge in several fields with a special emphasis on the molecular events involved in the adaptation of anaerobes to oxidative stress. The structural group eventually split in two teams, respectively devoted to biomolecular NMR and bioinformatics-chemoinformatics, leading to the current organization in three teams. Team 1 is studying the adaptation of anaerobes to oxidative stress, team 2 is a structural biology team exploiting the NMR facilities of the IFR88 and the third team develops and exploits a bioinformatics-chemoinformatics platform devoted to studying protein/protein interactions (PPI) and designing compounds collections enriched in PPI inhibitors. This platform is part of the antiviral drug design AD2P IBISA national platform. The laboratory was confirmed as a CNRS unit in 2010 following its first evaluation by the AERES. In parallel, the University Aix-Marseille I has established an agreement with the laboratory for allowing the lab to welcome teachers as part as its permanent staff and to participate to its financial support. The laboratory is waiting to benefit from more workspace in order to increase its staff by welcoming new teams or reinforcing the already existing ones.

- **Management team**

Leader of team 2 is the head of the lab and manages the unit in an excellent atmosphere of collaboration, enhanced by the sharing of the labs and offices by all lab members. A directory board formed by the three group leaders that take decisions on scientific and financial priorities assists the head of the lab and a laboratory committee, which gathers representative of the permanent and non-permanent staff, discusses the general policy of the laboratory.

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	9	9
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	7	7
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.7 of the application file)	7	
N7: Number of staff members with a HDR or a similar grade	7	7

2 • Overall appreciation on the research unit

- **Summary**

This is a lab founded in 2008, which brings together three teams, with skills in biochemistry, structural biology and modelling, whose purpose is the study of biological responses and the design of modulators thereof. The first team is a thematic group dedicated to the study of anaerobic bacteria while teams 2 and 3 are devoted respectively to structural studies (NMR) and to structural bioinformatics and molecular modelling of protein/protein interactions and their inhibitors. The IMR possess excellent instrument resources and benefits from facilities of the federative institute (IFR88) to which it participates. The laboratory carries out its work in a remarkable collaborative atmosphere. However, its impact remains limited for the moment with publications mainly published in specialty journals. The visibility of two teams among three is essentially at a national level, with a very limited number of research grants and a deficit in student and postdoctoral fellows. The risk taking for the leaders that originated in the creation of the IMR must be acknowledged. Nevertheless, for the future, the absence of high-profile project(s) with sufficient critical mass and funding, and the dispersion of some of the research themes is not likely to quickly reclaim the undeniably strong expertise of its PIs.

- **Strengths and opportunities**

- A permanent staff, young and of undeniable quality with complementary technical expertise, assisted by a large technical staff (7 permanent technical staff for 12 researchers and teachers).

- Opportunities for excellent collaborations thanks to the biomedical environment and to the lab participation to the IFR88.

- Quality of the equipment and the technical platforms implemented by the lab members.

- Lab members share an excellent spirit of working together due to the strong commitment of the team leaders and particularly of the lab head.

- **Weaknesses and threats**

- Difficulties for two teams to obtain sufficient research grants that threaten the long-term feasibility of projects despite the support from CNRS and University.

- Insufficient maturity of the project leading to a lack of a shared vision about the common scientific future of the three teams with difficulties in prioritizing projects.

- Low productivity considering the number of full-time researchers present in the laboratory.

- Current space limitation, which is an obstacle to further development.

- **Recommendations**

- The laboratory must absolutely bring forward one or more key projects that will lead to significant funding and will provide the visibility needed to integrate in national and European networks.

- The laboratory should now deviate from a strategy based to date on recruiting permanent research/technical staff and move towards a working model based on attracting external students and postdocs.

- **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	3
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	7
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	0.83
A4: Number of HDR granted during the past 4 years	4
A5: Number of PhD granted during the past 4 years	6

3 • Specific comments

- **Appreciation on the results**

The research performed by the unit is solid and convincing in at least two directions: the stress response of anaerobes and the search for inhibitors of protein-protein interactions (regular interactions and those involving disordered regions. Interesting work is also ongoing in the field of cell/cell interactions involved in preB receptor activation.

During the last period (2006 to 2010), the laboratory had a somewhat limited production with 51 papers published, often in specialty journals, of which 30 originating from the lab (First and/or last author belonging to the lab). Major articles are 1 PNAS, 2 J Mol Biol and 1 JBC. In addition laboratory members participated to 1 Embo J and 1 patent was filed during the period. It should however be noted that several staff members only joined the laboratory in the second half of this period and a number of them are involved in teaching.Although fair, obviously this production does not reflect the expertise of the lab members in domain such as anaerobes and NMR studies that was acknowledged by the committee members. Given the number of permanent staffs (12 in 2010 and 7 technical staffs) and the

technologies available to all teams, higher impact publications could be expected. This deficit might be partly explained by the difficulties encountered in 2008 during the clustering of the three teams in common lab facilities. Concerns about productivity were made during the first assessment of the laboratory two years ago. The 2009-2010 period saw however an increase of the amount of publications by the teams (from 4 publications in 2008 to 14 in 2010). One may also note a continuation of this recovery in 2011 as several publications are accepted for publication in good journals (1 JBC), as noted from the results that were presented.

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

There were about twenty talks given abroad upon invitation (international meetings and invited conferences) but most can be ascribed to team 3. Five PhDs were defended during the period and 4 are currently ongoing. The laboratory shows a serious shortcoming in the recruitment of Post-docs, which is low even for French standards (2 Post-docs during the period). Conversely, the team managed to attract several technical persons (1 TCN CNRS in 2009 and 2 TCN CNRS in 2010) and an assistant professor MCF (2009), confirming that the lab working model was so far more geared toward hiring permanent rather than non permanent people. The lab has succeeded in raising more than 899 k€ in 2006 to buy a new NMR spectrometer, which is a very nice achievement and has boosted the NMR infrastructure in the region. However, except for team 3, the IMR has not been successful yet in raising other funds since, in particular from ANR.

The laboratory has long established national and international partnerships with collaborations in Canada, USA, UK, China, Greece and Portugal, but these collaborations did not translate into internationally funded projects and in particular no European network was noted. Team 3 still participates to the national research network (GDR) “Chemoinformatics”.

On the other way around, the laboratory is well inserted locally with its participation to the IFR 88, for which team 2 is the scientific administrator of the NMR facilities, and the implementation of the drug design platform operated by team 3, which is part of an IBISA labeled national platform for drug screening. Moreover, teams 2 and 3 have participated to the regional proposal for the French call ‘Investissement d’avenir’, evidencing its regional visibility as a structural biology laboratory. From this standpoint, University Aix-Marseille I has stressed its local support to this unit.

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

The laboratory must be credited of the real investment of its members in teaching duties. Not only teachers but also all scientists are involved in teaching. In particular, an educational track in biochemistry was set up by lab members and the laboratory hosts several ATER, all of this being well appreciated by the University. The lab has been successful in attracting young researchers with complementary expertise. The audition with the permanent and temporary staff has pinpointed the very goof spirit and collaborative mood of all lab members. Students are given the opportunity to present their work on a regular basis, in group, lab and IFR meetings and are encouraged to present their work in national meetings. Credit for the excellent spirit in the IMR is to be given to the director who took a personal risk by creating this laboratory.

- **Appreciation on the scientific strategy and the project**

The IMR created in 2008 is held in common premises since 2009. These surfaces currently too limited for allowing the extension of the laboratory, are expected to increase in 2012. In this context, the laboratory wishes to develop its activity toward an integrated structural biology approach by building on technological approaches either available owing to the IFR, or to be acquired soon such as SAXS, fluorescence polarisation fluorimetry and titration calorimetry. In the field of microbiology, interdisciplinary projects should be strengthened around the thioredoxin system in order to develop modulators with antibiotics potential. With regard to the activities on eukaryotes, the projects will focus on collaborative work with both the Canceropôle for the continuation of the work on molecular interactions involved in oncogenic process, and with local virologists in order to design novel antivirals targeted against emerging viruses. To carry out these projects, the lab expects to attract two young researchers for teams 1 and 3 and also considers the possibility of a professor to reinforce the chemoinformatics part. During the last period, the lab has hired three permanent technical staff. IMR intends to recruit two additional engineers, the first one to balance the expected retirement of a biochemical engineer and the second to gain a new technical expertise in proteomics analysis. This

scientific strategy is consistent with the current activity of the lab. In particular, the project relies heavily on the bioinformatics platform and the expertise and facilities in NMR, which are strengths of the lab. Yet, it relies too much on the, always uncertain, hiring of permanent people rather than on the recruitment of Post-docs. Furthermore, sustainability of choices is very uncertain due to a lack of funding for most projects. From this standpoint, common projects irrigating several teams constitute a basis for integrated project that should help refocusing the activity of the lab in order to define a few cutting-edge projects and to define a common view of the future of the lab.

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

TEAM 1

- **Title of the team and name of the team or project leader**

Functional Genomics of Anaerobiosis – Alain DOLLA

- **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)	4	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)		
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	
N7: Number of staff members with a HDR or a similar grade	3	3

- **Appreciation on the results**

This team is led by a DR2 CNRS and comprises 3 CR1 CNRS and 1 MCF.1 A TCN will join the team for the next period. This team studies the aspects related to the molecular and cellular factors linked to life in the absence of oxygen. Two biological models are used, the anaerobe bacteria *Desulfovibrio vulgaris* and *Thermotoga maritima* respectively. The first one is a sulfate reducer bacterium that has been studied for a longtime by the team. Two themes are developed: 1/ the adaptation to anaerobiosis and 2/ the response of anaerobic bacteria to oxidative stress. The latter is subdivided in i) global response to oxidative stress, ii) membrane oxygen reductases and iii) thiol redox system. The team uses global approaches such as proteomic and genomic analysis and collaborates with team 2 for the structural aspects. Many international teams are trying to explore this topic as well, which is important not only for understanding how the anaerobes manage a protective effect under oxidative stress but also from an evolutionary point of view.

The productivity of the team is rather low with regard to its composition. Team members have co-authored 16 papers over the past period, of which 8 from the team (first or last author), 2 book chapters, 4 on other lab projects and 2 on external collaborations, in general (1 J Mol Biol, IF 4.0 and Biochemistry, IF 3.2) and specialty journals (Environ microbial, IF 4.9, biochemistry, FEMS microbiol letters IF 2.1). Several publications are however currently in press or under review.

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

The group has long-standing local and international collaborations (Portugal, Canada, USA), but they do not participate in any national or international networks although collaborations with strong groups within the field have resulted in 4 collaborative papers. Team members were invited to only one international conference held in Tomar, Portugal on Microbial Respiratory Chains and 1 French thematic school. They have participated in several National and international meetings (20 communications out of which 5 were oral presentations).

The group attracts PhDs students and undergraduate students in limited numbers. 2 PhD have defended their thesis and the team has hosted 7 master students. 4 post doc fellows were recruited but for very short periods. 1 PhD is ongoing.

The group has a poor record in raising research funds. 2 grants, of which one ANR project as partner was obtained during the period 2005-2007 and one collaboration is currently funded by a Portuguese fund. They have however as partner a private company that is financially supporting their studies.

- **Appreciation on the scientific strategy and the project**

Four main themes are proposed for a project, which is the continuation of the previous activities. The main research axis concerns 1/ the study of the membrane-bound, cytochrome C and quinol bd oxidases by using deletion mutant strains and trying to identify putative partners potentially implicated in the transfer of electrons, 2/ metabonomics studies of the oxidative stress by using NMR in collaboration with team 2, including the study of the thiol-disulfide redox systems in Desulfovibrio 3/ The study of the transcriptional regulation linked to the orp complex and 4/ the functional characterization of both Termogata maritima and Desulfovibrio vulgaris proteins of unknown functions. The project is well organized and may have potential for biotechnological applications. For instance, the discovery of the function of proteins encoded by genes of unknown function is original and important for the field. It is nevertheless highly competitive and depends on human resources (preferentially Post-docs). Results were recently obtained (2 papers in press, and one submitted to J. Bacteriol.) warranting the interest of pursuing the project. Yet, it must be noted that the funding is not yet secured for ongoing and future projects (1 ANR project submitted).

- **Conclusion**

— Summary

The past, current and future research program is solid science that involves interesting aspects of the biology of anaerobiosis. The group seems to be well organized with several collaborations and each leader develops complementary approaches and subjects. A strong collaboration has been established with team 2 on the metabonomics aspects although there is a lack of human resources to undertake efficiently this part of the project. However, the productivity and the lack of financing support is worrisome. The recent beginning of improvement in the publications records is however encouraging and might be of help in the search for financing supports.

— Strengths and opportunities

- Experience of the PI and his 4 co-workers in several aspects of oxidative stress and anaerobiosis and functional characterization in general.

- Some originality of the project in spite of the competition.

— Weaknesses and threats

- Productivity should increase.

- No involvement in networks.

- Absence of a funding policy.

— Recommendations

- Take advantage of the expertise to actively seek more collaboration at international levels that can support funding and increase attractiveness.

- Increase the number of research papers.

- Reinforce the recent extension of studies at genomic level that was well appreciated by the committee.

TEAM 2

- **Title of the team and name of the team or project leader**

NMR of Molecular assembly – Françoise GUERLESQUIN

- **Staff members**

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

- **Appreciation on the results**

The team is led by a DR1 CNRS and is composed of 1 CR2 CNRS, 2 MCFs and 2 IR2 CNRS. The team uses NMR spectroscopy to study signal transduction pathways associated to cell response. Along this topic, the following three research lines are followed: 1/ Molecular basis of preB cell receptor activation, in particular structural studies of galectin-1 – oligosaccharide interactions with a collaboration with team 3 for the study of galectin-carbohydrate interactions 2/ Signal transduction with structural studies of the ErbB2/MEMO complex involved in breast cancer and metastasis formation, 3/ cell response using structural studies of the thioredoxin/thioredoxin reductase system in the anaerobic metabolism of *Desulfovibrio* in collaboration with team 1. All three areas fit in the general research line of the unit (interaction and modulation of response), with the third one being a transverse topic in the unit.

The group and group members have published 19 papers over the past period, of which only 6 manuscripts from the group (first or last author) and 2 with the PI as the last author. The highest impact papers are co-authorships (1 PNAS and 1 EMBO J.). This productivity is not particularly high. One patent was filed with the PI of the new team 3. It should be noted that the two MCFs have their regular teaching duties and two lab members (1 CR2 and 1 MCF) only joined the team in the second period of this evaluation (2008 and 2009, respectively).

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

Team 2 is collaborating with the other two teams of the unit in almost all projects, playing thus a central role in structural, interaction and, recently, metabonomics studies by NMR. Most external collaborations are at a national level, except for one with a lab in Greece. There is no participation to EU programs or international networks.

The group members have a good national visibility and a limited international visibility. The CR2 has given a lecture at one international conference (Gordon Research conference) and team members attended 7 international conferences. There is a fair number of presentations and posters at national and international conferences (16 communications). The head of the team has chaired sessions at international conferences.

Nevertheless, it must be stressed that this team resulted from the splitting in 2008 of the former NMR group led by the lab head into teams 2 and 3. Most of the successes of team 3 must therefore be ascribed in equal part to the PI of team 2, who is occupied with the administration of the unit and whose dedication to bring out an effective structure has to be acknowledged.

The group actively recruits and trains PhD and Master students. 4 PhD students have defended their thesis and 2 fellowships are ongoing. However, most students and Post-docs are French with only one foreign post-doc for a short period under an Erasmus program. This team is strongly involved in teaching.

The group has a low record in raising research funds with only 1 ANR grant (2005-2007) 1 INCA (2005-2007) and 1 CNRS PEPS (2010). However they managed to obtain 840 000 euro to buy a new NMR instrument in 2006 (600 MHz with cryoprobe), which represents a very nice achievement and boosted the regional NMR infrastructure.

- **Appreciation on the scientific strategy and the project**

The projects of the past will be extended and continued on the following directions: 1/ pre B cell receptor activation. Preliminary results suggest that the lambda 5 region contacting the VpreB protein is not structured in its isolated form and only becomes structured upon binding. Therefore one goal is to obtain the structure of the complex, which is technically difficult because of its large size, therefore requiring differential labelling techniques. 2/ The second project concerns the study of the ERB2 C-terminus interaction with Grb2, Shc – extended from MEMO interaction. 3/ The third project concerns the identification of the glycosylations of the pre-B and stromal cells by a novel lectin microarray method to identify the specific galectin-1/carbohydrates interactions involved in those cell/cell interactions that will be further studied by NMR. 4/ finally, the NMR structural studies of the thioredoxin reductases will be pursued with the ultimate goal to find ligands that could interact with TR3 but not with TR1 in order to affect specifically the TR3-dependent system. Other thioredoxin-like proteins might be studied depending on collaborations within the IFR88. The continuation of the research program suffers from a lack of focus and strategic choices. Part of this might be attributed to the central role played by team 2 in structural studies in the projects of teams 1 and 3, which might result in a large spread of the rather limited human resources, preventing focusing on a few key topics. Another cause lies in the recent arrival of its young members, involved so far in different projects. Nevertheless, the team considers identifying some priorities depending on its future human and financial resources. For instance, the Erb2/MEMO project could be stopped once completed, although its implications for cancer might make it a particularly interesting project.

- **Conclusion :**

— Summary

The research carried out by this structural team is sound and presents interesting aspects for instance the ones focused on signal transduction during pre-B cell activation. The team holds a pivotal NMR expertise and the record of the PI and the new composition of the group should warrant future results. However, because of the centrality of this group and owing to its recent splitting, its projects are quite scattered. Moreover the group lacks originality and a clear vision for the future, in part because of its recent restructuring. Therefore, there are opportunities for defining more ambitious projects.

— Strengths and opportunities

- Experience of the PI and her co-workers in NMR.

- Pivotal role in the unit and multiple collaborations with other teams.

- Central role in regional NMR infrastructure.

- Opportunity to integrate projects within the biomedical environment.

— Weaknesses and threats

- Limited size of the team with regard of the involvement of two permanent scientists in teaching and one engineer in NMR service activities.

- Lack of a high-profile project.

- Limited productivity even if the nature of structural studies of complexes puts some limitations.

— Recommendations

- Increase funding and international visibility.

- Make better use of expertise by actively seeking collaborations for example in the field of B cell immunology.

- Try to attract more research staff or post-docs to counter balance the rather large service part of the unit.

TEAM 3

- **Title of the team and name of the team or project leader**

Interactions, Dynamics and Drug Design – Xavier MORELLI

- **Staff members**

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

- **Appreciation on the results**

This team is headed by a CR1 CNRS and comprises 2 CR1 CNRS, 1AI CNRS and 1 TCE CNRS. The group was created in 2008 by splitting from the structural biology group (team 2). Another PI joined the group in 2008. The team is using molecular dynamics, biophysical methods (eg, SAXS, NMR) in collaboration with team 2 and chemo-informatics approaches to understand molecular determinants at the atomic levels of protein-protein interactions and to design small molecules capable of interfering with these interactions on a selected number of targets. The team has built the Gis-IbiSa INT-3D platform in collaboration with several other platforms located in different sites in Marseille. INT-3D carries out *in silico* screening on several protein complexes important in cancer and infectious diseases. Successful identification of hit compounds has been reported and an interesting database of protein-protein complexes has been implemented online. The team has external collaborations, essentially in the field of drug design and some structural bioinformatics projects are performed in collaboration with scientists of the lab. Three research themes have been specifically undertaken 1/ protein-ligand interactions (e.g., Galectins) and conformational changes upon protein-protein complex formation (e.g., TolAIIIc-G3PN), and the adaptation of psychrophilic micro-organisms to low temperature (e.g., thioredoxin-thioredin reductase), 2/ macromolecular recognition in intrinsically disordered

proteins (e.g., BCR-ABL), and 3/ Modulation of protein-protein interactions (eg., Nef-fyn, HCV, measles virus, prostate cancer…) and analysis of the interfaces (the 2P2I database).

The team has a good production in term of publications with 25 articles and reviews, of which 1 PNAS, several Proteins, 1 J. Chem. Inf. Model, 1 JBC, 1 Biochem. J. The team has also filled 1 patent application in the area of infectious diseases.

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

The team has successfully secured national funding during the last period: 1 Young scientist ANR, 2 ANR participations, 2 ANRS grants, and 1 FRM grant. 3 PhD fellowships from the region and the French embassy and 1 industrial contract were also obtained. However, like teams 1 and 2 there is no international or European grants. Team members gave 42 seminars of which 8 invited international conferences. There is a significant implication in teaching.

During the last period, the group ran on 4 permanent staff members (3 researchers and 1 permanent technical staff), non-permanent technical staff member and 2 postdocs (one national and one international) 2 students have defended their thesis and two PhDs are currently ongoing. 2 other two-year post docs (national) have been recently hired.

- **Appreciation on the scientific strategy and the project**

Team proposes 3 major projects: 1/ development of computational methods that aim at predicting whether a protein-protein interface is drugable or not 2/ design of PPI focused compound collections 3/ screening with in silico and in vitro (collaborations with experimental groups) methods several protein-protein interactions: nsp10-nsp14 from SARS (infectious disease, search of hit compounds, in collaboration with team 2 and several groups in Marseille), the thioredoxin-thioredoxin reductase system (chemical biology, tools to study metabolic pathway, in collaboration with teams 1 and 2), Bcr-abl (leukemia) and Hsp27 (prostate cancer). This latter project involves the development of the SAXS expertise by the CR who recently joined the team. The continuation of the research program includes cutting edge technology, in particular a virtual screening platform that should be further developed. The other projects described briefly are more mainstream. The future theme of the new group covers many biology fields by addressing protein-protein interactions. Antiviral drug design seems to emerge as a leading project thanks to collaboration with a structural virology lab in Marseille.

- **Conclusion :**

— Summary

This group emerged from a restructuration of Team 2 in 2008 and developed an integrated structural bioinformatics-chemoinformatics platform that yielded original results in the field of PPI pharmacology (label IBISA). It provides service to the community and in silico methods implemented online that help predict if a protein interface is likely to be druggable. This group has been mixed together in particular by incorporating a new PI bringing a SAXS expertise and it has still to demonstrate the value of the integration of all group members into a common project that goes beyond a common interest in biophysical techniques.

— Strengths and opportunities

- Combination of several in silico and experimental approaches.

- Very challenging biological systems.

- Financial supports obtained for several screening projects.

- State of the art computers and software packages are used.

- Interactions with pharmaceutical companies.

- Novel SAXS expertise in the unit, very complementary to NMR.

— Weaknesses and threats

- A variety of projects lacking a clear direction to be followed.

- Unclear strategy to reinforce the team, somewhat in opposition to the will of welcoming new teams.

- Future of the platform (within or not the laboratory) not completely defined.

— Recommendations

- Focus on ambitious questions with potential impact in the biomedical field.

- Identify a project that will combine efficiently all expertises of the team

- Define a clear strategy for downstream work once targets and lead are identified.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
UPR3243 - INTERACTIONS ET MODULATEURS DE RÉPONSES.	**B**	**B**	**A**	**B**	**B**
FUNCTIONAL GENOMICS OF ANAEROBIOSIS [GUERLESQUIN-DOLLA]	B	B	Non noté	B	B
NMR OF MOLECULAR ASSEMBLY [GUERLESQUIN-GUERLESQUIN]	B	A	Non noté	B	B
INTERACTIONS, DYNAMICS AND DRUG DESIGN [GUERLESQUIN-MORELLI]	A	A	Non noté	A	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**
  - **SVE1_LS7 Recherche clinique, Santé publique**
- **SVE2 Ecologie, environnement**
  - **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
  - **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
  - **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

CENTRE NATIONAL
DE LA RECHERCHE
SCIENTIFIQUE

Unité Interactions et Modulateurs de Réponses
Institut de Microbiologie de la Méditerranée
Directeur : Françoise Guerlesquin

Answers to the AERES report on UPR3243

Concerning AERES Evaluation:

As a general remark, we consider that the criteria used for AERES evaluations do not take into account the risk to develop a *ex-nihilo* created laboratory. Most of the researchers of our laboratory have operated a thematic change in 2008, between prokaryote and eukaryote systems. Such changes are obviously associated to a decrease in productivity. In consequence, three years of existence are not sufficient to provide a satisfactory activity report regarding the AERES criteria. Moreover, we think that newly recruited researchers should not be evaluated using the AERES defined "*member active in research"* criteria.

Concerning the committee report:

1- The committee noted: "*The laboratory should now deviate from a strategy based to date on recruiting permanent research/technical staff and move towards a working model based on attracting external students and postdocs"*. Our first goal was to reinforce the permanent staff of the laboratory following the previous recommendation from the AERES committee in 2009. In that respect, we welcomed 3 new researchers and 4 technicians in the last 3 years demonstrating the attractiveness of our new laboratory. We agree with the present committee that recruiting students and postdocs is now our priority.

2- Team by team comments:

Team 1 mostly agrees with the committee conclusions. However, regarding the weaknesses and some comments raised by the committee, we would like to clarify several points:

1- The productivity of the team as indicated in the document sent to the AERES in December 2010 corresponded to 18 co-authored papers, and not 16 as mentioned in page 8 of the AERES report. In addition, we indicated to the committee during the visit in January 2011 that 5 additional papers were in press at that time (among them 1 JBC and 1 Environ. Microbiol. for which the team members are first and last authors). Even if one can consider that this scientific productivity of the team is "*rather low with regards to its composition*" we want to stress that the team was combined from four different teams in January 2008. Moreover, two of these researchers came from completely different research fields (GB was working on yeast respiration and CA on aerobic hyperthermophile microorganisms). This thematic reconversion, that must be acknowledged, explains the decrease in productivity and should have been considered for this evaluation. We thus acknowledge the committee that noted a "*recent beginning of improvement in the publications records*".

31, CHEMIN JOSEPH-AIGUIER – 13402 MARSEILLE CEDEX 20 – TÉL. 04 91 16 43 79 – TÉLÉCOPIE 04 91 16 45 40 - e.mail guerlesq@ibsm.cnrs-mrs.fr

It should be also noted that even if the committee considers that the researchers are "*assisted by a large technical staff*", team 1 benefits from only one TCN to assist directly five permanent researchers (1DR, 3CR and 1 MCF). This ratio is much lower than the one generally found in INSB research teams.

2- As weaknesses, the committee raised also the absence of involvement in networks. We consider this statement erroneous since the team has obtained two research contracts with a Portuguese partner from the University of Lisbon as indicated in the report document. Nevertheless, we agree with the committee that it should be improved.

3- The committee noted : *"Absence of a funding policy"*. We disagree with this statement as the team policy is to apply for various grants but raising funds in fundamental microbiology is restricted compared to biomedical research field. Collaboration with the two other teams will help and strengthen our efforts for the next years.

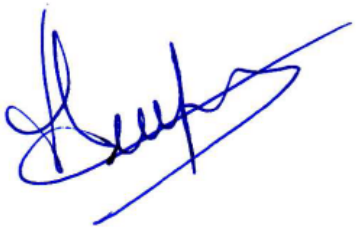
Team 2 mostly agrees with the committee conclusions

1- However, we noticed some incoherences in the report. As an example the committee pointed out that *"The group has a low record in raising research funds with only 1 ANR grant (2005-2007) 1 INCA (2005-2007) and 1 CNRS PEPS (2010)."* But just after noticed that *"they managed to obtain 840 000 euro to buy a new NMR instrument in 2006 (600 MHz with cryoprobe), which represents a very nice achievement and boosted the regional NMR infrastructure."*

2- The committee indicated that "*Moreover the group lacks originality and a clear vision for the future*." We fully disagree with this statement. First, we are developing very new NMR approaches among them segmental labeling and protonless NMR, which are necessary to investigate large protein complexes. Second, we focus our projects on cell signaling, involving cell-cell interaction and signal transduction that we consider as high profile projects.

Team 3 agrees with the main recommendations from the committee. However, concerning the weaknesses *"A variety of projects lacking a clear direction to be followed"* we would like to emphasize that the group has two clear directions for the future: i. development of chemoinformatic tools for targeting protein-protein interfaces and ii. experimental-based identification of anticancer and antiviral active compounds on challenging biological systems.

Marseilles, April 11th, 2011



Françoise Guerlesquin