BSC - Biotechnologie et signalisation cellulaire

Rapport Hcéres

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

Research Units Department

AERES report on unit:

Biotechnologie et Signalisation Cellulaire

Under the supervision of the following institutions and research bodies:

CNRS

Université de Strasbourg

January 2012

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

Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head

Pierre Glaudes

Unit

Name of unit:	Biotechnologie et Signalisation Cellulaire
Acronym of unit:	BSC
Label requested:	UMR
Present no.:	7242
Name of Director (2009-2012):	Mr Jean-Luc GALZI
Name of project leader (2013-2017):	

Members of the committee of experts

Chair:	Mr Stefano MARULLO, Paris
Experts:	Mr Philippe LEFEBVRE, Lille
	Mr Eric REITER, Nouzilly
	Mr Alain CHARIOT, Liège, Belgium
	Mr Andreas G LADURNER, Münich, Germany
	Mr Dennis J McCANCE, London, UK
	Mr Frank STUBENRAUCH, Tübingen, Germany
	Mr Martin WELSH, Cambridge, UK
	Ms Solange MORERA, Gif sur Yvette (CoCNRS representative)

Representatives present during the visit

Scientific Delegate representing AERES:

Mr David DOMBROWICZ

Representative(s) of the unit's supervising institutions and bodies:

Mr Eric WESTHOF, Université de Strasbourg

Mr Jean-Claude MICHALSKI, INSB, CNRS

Report

1 • Introduction

Date and conduct of visit:

The visit of the unit took place on January 24, 2012.

The agenda was the following: 1. Plenary session with all members of the laboratory: -"historical" overview of the laboratory and of its past achievement by the current and future Director and general presentation of the project to come; -achievements/project presentation by the PIs of the 7 teams composing the laboratory. 2. Discussion with the representatives from CNRS and the University of Strasbourg. 3. Group discussions with students/post doc, technicians/engineers and researchers with permanent position. 4. Closed-door meeting of AERES committee.

It shoud be noted the the organization of the day and the quality of the documents were excellent, and that the general atmosphere was constructive and informal throughout the duration of the visit.

History and geographical location of the unit, and overall description of its field and activities:

Geographical location

The laboratory "Biotechnologie et Signalisation Cellulaire", UMR 7242, is located on the Illkirch campus, in between the IGBMC and the School of Pharmacy. As described below, this location explains the multiple sustained collaborations existing with the teams from these institutions. The campus also hosts a number of start-ups and research agencies. The laboratory is located in the building of the Engineering School of Biotechnology of Strasbourg and the principal Professors of the School are also members of the laboratory.

History

The research center in the School of Biotechnology started in 1995 with three independent laboratories merged into a single CNRS laboratory (UMR 7100) in 2004. A subsequent operation consisted in the merging of the UMR 7100 with the three other laboratories of the School of Pharmacy to create the Laboratoire commun 1 (UMR 7175). The idea behind this vast regrouping was to promote a "Drug Discovery Center", to integrate research, teaching, technology transfer and technical platform components "from genes to drugs". This initiative was partially successful. On one hand, after the evaluation by AERES in 2008, the CNRS decided to create four laboratories at the end of the four-year (2005-2008) contract of the UMR 7175; the teams at the School of Biotechnology went through a long process of reorganization, marked by the interruption of multiple projects (causing merging or leaving of several teams); the laboratory UMR 7242 "Biotechnology and cellular signaling" was finally created by the CNRS under its current configuration. On the other hand, the original seeding idea of the drug discovery center grew up and eventually resulted in the LabEx project MEDALIS (see below), which was selected for funding.

Field and activities

The research topics of the laboratory focus on protein-protein and protein-nucleic acid interactions ; each team works either on replication, transcription and genome integrity, or on transmembrane signaling. These two research axes are reflected in the organization of the laboratory around two official themes: **"Genome Integrity and Tumor Biology"** and **"Receptors, Membrane Proteins and Therapeutic Innovation"** grouping four and three teams, respectively.

The technical approaches are at the interface of integrative biology approaches (mouse homologous recombination and phenotyping), biological chemistry (screening compound libraries, development of pharmacological tools with therapeutic potential) and biotechnology. Whenever possible, translational research project are conducted mostly in collaboration with startups or companies. It appears quite clearly that the research topics and the high commitment to translational science are markedly influenced by the overlaps with the Engineering School. Also technical expertise in chemical and structural genomics and research projects are

shared with the neighbor School of Pharmacy and IGBMC. Scientific interaction with teams in these institutes is strongly encouraged.

The laboratory has established (or contributed to establish) high-level technology platforms for screening, drug technologies, analytical chemistry, imaging, animal model production, phenotyping of genetically modified animals, structural biology, protein production, many of which are hosted in its building. Technical facilities and platforms are open to both academic and industrial groups.

Management team:

The current head of the laboratory has been elected to continue his function for the term to come. He is apparently well appreciated by colleagues, technicians and students. The director meets with administrative persons weekly for regular administrations of the lab. Once a month, a meeting with the PIs of the seven teams is organized to debate and decide about all scientific issues. A "laboratory council", also including representatives of technicians, students and post-docs, takes place every 3 months to debate funding issues, careers (technical employees), student and pos-doc hiring and training. The General Assembly of all laboratory members is organized twice a year. Finally, an advisory scientific board is organized with external members (it is not clear how this is done) every two years.

Unit workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	9	8	8
N2: EPST or EPIC researchers	25	22	20
N3: Other professors and researchers	10	10	4
N4: Engineers, technicians and administrative staff *on a permanent position	17,70	17,20	
N5: Engineers, technicians and administrative staff * on a non-permanent position	6		
N6: Postdoctoral students having spent at least 12 months in the unit	18		
N7: Doctoral students	23		
N8: PhD defended	27		
N9: Number of Habilitations to Direct Research (HDR) defended	3		
N10: People habilitated to direct research or similar	24	25	
TOTAL N1 to N7	108,70	57,20	32

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the [01/01/2007-06/30/2011] period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

2 • Assessment of the unit

Overall opinion on the unit:

The research done by members of the unit is globally of very high quality in both basic and translational science. The marked reorganization of the unit following the previous evaluation is a success. Because of historical reasons and also due to the connection with the Biotechnlogy School, which requires a large coverage of scientific approaches, quite diverse research topics have been developed in the Laboratory. Diversity in topics, in the various projects proposed by each team, and in all other multiple activities, networks …are a hallmark of the Unit. Diversity is an opportunity but may also prevent the achievement of the internationally-recognized status that this Laboratory could probably obtain. In its future strategy, the Laboratory should consider the implementation of progressive scientific convergence (the technical cohesion already exists) and the teams should focus on a more restricted number of projects.

Strengths and opportunities:

The Laboratory is located in an exceptional environment for both high quality basic science and applied science. Funding is globally sufficient, international collaborations and networks are quite numerous (including the Medalis affiliation for 3 teams), the connection with the University and the Biotechnology School provides well-trained and motivated students.

A number of high quality technical facilities are available, which in particular cover nearly all aspects of the drug-discovery process.

Weaknesses and risks:

Relatively little focus and the absence of critical mass around common inter-team core projects have been mentioned above. In the current economic climate with threats on funding, recruitment and retention of permanent staff, more focus and scientific convergence might rapidly become critical to survive in the international competition.

Restructuring has led to recomposition of teams with a very large amount of permanent scientits, which, by consequence, perform relatively less compared to more “classical” teams.

Overall, there are excellent opportunities for translational science for which it is difficult to determine how successful it will be in the absence of a well defined managerial process. For example, in Drug Discovery process it is not clear (1) what steps are in place to chose the targets to be followed up, (2) where the biology will be carried out, (3) who monitors milestones in the drug discovery pipeline, (4) who decides to cut programs, and (5) when they license a drug.

Recommendations:

Try to evolve to better inter-meshed groups of equivalent size within the unit.

Foster interaction between the existing teams within the unit, especially with regards to the identification and research exploitation of common interests.

3 • Detailed assessments

Scientific quality and production:

Globally during the past four years the laboratory published 182 articles (including 50 signed by PhD students as first authors) and 25 invited reviews or book chapters. Sixty per cent of the articles were published in journals with IF >4 and the number of publications in journals with IF>10 doubled (21 vs 10) during this period of time compared to the four preceding years. Lab members gave 270 invited talk/seminars. Research themes are globally original, and some groups were clearly leaders in their specific field. The team by team analysis (below) shows heterogeneity in the average quality of publications.

Translational research is generally very good (as evidenced by 13 patents and 5 licenses). As this Unit also generated several publications in highly ranked scientific journals, it is a major accomplishment. However, it was not clear how drug discovery is managed once a drug discovery program is started. For instance, in the Medalis Drug Discovery Centre (Labex) it is not clear (1) what steps are in place to monitor milestones in the drug discovery pipeline, and (2) who decides to cut programs (collaborating companies or Medalis).

Integration into the environment:

This item corresponds to the strongest asset of the laboratory. The laboratory has shown sustained commitment in translational research, interaction with start-ups and pharmaceutical companies (joint research programs, contracts) and research valorization. Twelve patents were filed (five under license), and several « products » are on the market, consisting in peptides, antibodies or chemicals for biotechnological or pharmacological research. Private contracts and consulting activity represent a significant proportion (20-25%) of the financial resources of the laboratory. During the past 4 years the laboratory globally obtained 7 M€ of grants to be compared to the 1.3 M€ of institutional money. The academic grants were obtained by applications to both French and international calls. In most cases the funded studies were collaborative involving teams of the laboratory and external teams. In more than 50% of the cases, funding through collaborative grants was obtained from institutional French agencies (ANR, INCA, ANRS..). Principal investigators of the laboratory are often principal coordinators the collaborative study. The laboratory also received support for open technical platforms and bio-resources: Impress (membrane protein purification and structural studies); Techmed (in vivo assessment of drug absorption, distribution, metabolism excretion..); 3I (single chain antibody library for biotechnological applications); the national repository of Pseudomonas and siderophores. Finally, 3 teams of the Laboratory belong to the 10 founder teams of the "Medalis" Labex, which will be supported for a period of 10 years to identify and test drug candidates on validated targets.

Notoriety and drawing power:

Some indicators of the Laboratory reputation have been detailed above, such as the number of invited lectures and the coordination of collaborative studies. Four teams of the laboratory participate in international programs (2 European FP6, COOP, CEFIC-LRI, Interreg IV), one team obtained a grant from the NIH, and nearly all teams (except that headed by the recently arrived young investigator) are involved in multiple international networks (n=11). The laboratory did attract 2 young investigators who obtained ATIP/Avenir grants, the last one having joined the Lab in 2011. Post-docs represent approximately 15% of the work force of the Laboratory. Most of them were recruited locally.

Governance and life:

Credit should be given to the Laboratory and to its management for the pretty successful reorganization, which was conducted in two years, based on the results of the previous AERES visit. The task was certainly not simple. Despite these difficulties, the management could convince an outstanding young scientist to join the laboratory and to build a promising new team. It appears quite evident that the members of the laboratory are happy to work in the laboratory and to take advantage of the rich scientific and technological environment of the Illkirch campus. Inter-team technical collaborations are multiple and compensate for the relatively weaker scientific collaboration explained by the diversity of research themes. Diversity appears indeed one of the main characteristics of this Laboratory: diversity of research topics, diversity of the projects in each team, diversity of the networks, diversity of the technical approaches, diversity of the activities, diversity of the partnerships. If on one hand this diversity creates opportunities, on the other hand it likely represents an obstacle to major achievements, which usually are fostered by focusing on specific strategic objectives. The overall appreciation of

the laboratory is very good, but there is evident potential for further improvement in both scientific and translational activities, provided that the management would be more pro-active in focusing the efforts on well-identified priorities. In this context, the creation of an external biotechnology advisory board (not only that of the Medalis labex), including academic scientists and professionals of drug discovery, could be useful for strategic decisions concerning all the drug discovery-related activities of the laboratory.

Strategy and 5-year project:

The proposed scientific projects for the 5 years to come are in general original, scientifically sound, and some have potential high impact in science and/or health. The know-how, funding (Labex, ongoing grants, private contracts…) and the technical instruments (formed personnel, technical platforms, collaborations) for success are present. However, the number of projects in each team is often high, with a risk for dispersion and of loss of impact. No strategy has been presented to further increasing the critical mass of the laboratory in some specific research axis. The only announced strategic project in the years to come is the already funded creation of a new group in synthetic biology as an emanation of a Swiss laboratory from a prestigious institution (ETH, Zurich) in the context of a State-Region contract plan. Its director is an outstanding scientist and synthetic biology is a hot new topic, which fits perfectly in the context of a Biotechnology School. It is much less obvious how this new group might fruitfully collaborate with the projects of existing teams and improve their output.

Involvement in training:

PhD students and post-docs represent approximately 30% of the laboratory members. PhD students signed 27% of the published articles as first authors. One third of the permanent scientists of the laboratory are professors of the Biotechnology School. Thus the implication of laboratory staff in training is particularly high, both in Bachelor's and Master degrees and in the PhD program. The students have the unique opportunity of being in contact with a vast array of techniques in the School, in their training laboratory and in the technical platforms. In addition, students are permanently in contact with both basic and translational/applied science "cultures". A high proportion of students can find a position locally in the multiple startups collaborating with the laboratory teams. Most PhD students continuing in the academic research apparently remain in the area or in France. There are no numbers of how many former PhD students eventually obtained an academic position after the post doctoral training.

Analysis of technical facilities

The BSC Unit possesses several technical facilities. The Unit's main facilities include protein production platforms, analytical chemistry facilities, microscopy, equipment for molecular pharmacology, SPR equipment, a biophysics suite (fluorescence, CD etc), facilities for cell culture and finally, an animal house for mouse work. These standard common equipments are to be "managed" by a specific point of contact. The setup is fairly routine – a user reserves the equipment, is responsible for the equipment while using it, and pays a pro-rata fee for usage. Presumably, the unit gets some services such as DNA sequencing done locally but externally – it would have been of interest to have some information about what services are externalized, and how this is dealt with. The unit has a collection of national repository of Pseudomonas and siderophores.

The unit also integrates 2 platforms in addition to these common technical facilities:

1. The IMPress (Integral membrane proteins) platform dedicated to membrane protein (cloning, expression and purification). The platform will be opened to external clients very soon. It runs thanks to the involvement of 4 people including 3 technical staff sharing their time between the platform and a research team. A research director is of good advice for the construction of this platform.

2. The TechMed (technologies du medicament) platform dedicated to pharmacokinetic properties of active biological compound that could be used as medication. Absorption, distribution, metabolism, excretion and toxicity analysis are realized. The platform has been running thanks to a full-time non-tenured person since nearly 6 years.

Specific comments:

(1) Protein production/purification. The hardware is sound – exactly the sort of equipment that any laboratory wanting to do protein chemistry would need. However, no information was provided on, for example, frequency of usage of specific material, about potential equipment redundancy, future investment for replacement of aging material or acquisition of new equipment. For protein purification, it remained unclear whether users had to supply the columns/matrices or if they were available as part of the core facility and whether the facility was holding common stocks, a very useful resource.

(2) Analytical chemistry. UV-Vis HPLC, LC-MS and capillary electrophoresis systems etc. From the description, this looked less like a core facility and more like a well-equipped lab opening its doors to occasional users. Some indication of the level of usage (external to the lab that hosts the equipment) would have been informative in assessing the utility of this resource.

(3) Microscopy. Three fluorescence microscopes are described, and although one can image through z-sections, none appeared to be laser-scanning confocal units, which represents worthwhile equipment.

(4) Molecular pharmacology. A standard but essential equipment access is unrestricted to all teams.

(5) SPR and biophysical suite (combined). Hardware is sound (3 biacore devices, several fluorimeters etc) and access conditions are well defined. Since the teams are increasingly heading towards structural studies, maintenance of a strong biophysical suite will be of central importance. One missing item of kit is an isothermal calorimeter (to complement the Biacore).

(6) Cell culture. This is a core facility with a single point of contact. As expected, the hardware is distributed over several floors/labs, as appropriate.

(7) Animal facility. Facility is appropriate.

Summary and recommendations:

The teams within the unit should decide collectively what items of equipment they are likely to need for their 5-year plan. This is not clear from the descriptions provided. Concerning the TechMed platform, as this is of general utility to the Unit and external clients (academics or industries), it should be maintained.

4 • Team-by-team analysis

Team 1: Poly (ADP-ribosyl)ation et intégrité du génome

Team leader: Ms Françoise DANTZER & Ms Valérie SCHREIBER

Workforce

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	/	/	/
N2: EPST or EPIC researchers	3	2	2
N3: Other professors and researchers	/	/	/
N4: Engineers, technicians and administrative staff * on a permanent position	3	3	
N5: Engineers, technicians and administrative staff * on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	2		
N7: Doctoral students	4		
N8: PhD defended	3		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	3	2	
TOTAL N1 to N7	13	5	2

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the [01/01/2007-06/30/2011] period who will be present in 2013-2017.

Definition and downloading of criteria:
http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Scientific quality and production:

The team focuses its activities on the role of protein ADP-ribosylation, in particular the activities of the NAD-dependent poly-ADP-ribose polymerase family, a series of enzymes involved in DNA repair and genome maintenance. The field has been gaining anew in importance, in part thanks to the discovery of PARP1 inhibitors as effective anti-cancer therapy (albeit currently for a limited number of cancers, such as BRCA1-/- and BRCA2-/- breast tumors) and also to developments in the field, such as the identification of several additional proteins capable of specifically recognizing poly-ADP-ribose, of novel PARP targets, of crystal structures for several PARP family members, as well as of PARG, which the team also works on. Furthermore, novel imaging techniques in live cells have also added much benefit to the analysis. This has transformed the PARP field to one focused on genome maintenance to the broader topic of cellular signaling, since distinct PARP family members and PAR-recognizing proteins appear to have distinct cellular, molecular and physiological functions. The research activities of this team are at the center of these increased worldwide efforts to dissect the now much broader topic of poly-ADP-ribose signaling, possibly currently the least understood post-translational modification.

The team has been able to maintain and build on the global visibility of an existing team run by well recognized investigators. In addition, continuing the pioneering work on PARP1 and PARP2, the team has found interesting evidence for a role of PARG in DNA damage, showing that the absence of PARG causes increased radiosensitivity, indicating that PARG inhibitors could be therapeutically beneficial for cancer in combination with radiotherapy. Moreover, the group has ventured out to study the kinetics and mechanism through which PARP and other proteins recruit to DNA damage sites in live cells, studied the contribution of PARP1 and PARP2 to heterochromatin formation, the role of PARP3 and the macrodomain-containing PARP9 in double-strand break repair and mitosis. Moreover, the group has engaged in an additional series of non-local collaborations, in particular to study the connections between PARPs and metabolism: first by looking at the combined role of PARP1 knockouts together with other NAD-dependent enzymes, such as SirT1, a histone deacetylase, as well as identifying a metabolic phenotype in PARP1 and PARP2-deficient mice, which results from an effect of these mutants on SirT1 activity. The group published a large number of articles within few years (34 papers), most of which result from active local and non-local collaborations. These highly collaborative works, in particular, have led to publications in journals with very high impact (two papers in Cell Metabolism, one in J. Exp. Med., EMBO Journal and PNAS). Various group members also attend national and international scientific meetings mostly focused on PARP biology and genome maintenance.

Regarding translational research, PARP inhibitors are an obvious choice and this may be interesting if the biology holds up but as far as it can be determined, the biology of PARP-3 is not, as yet, well worked out. This team also developed new tools (antibodies and recombinant proteins) now being commercialized.

Integration into the environment:

The focus of the team on genome maintenance is of both basic and translational interest, as attested by funding received from organizations such as Ligue contre le cancer, EDF, as well as receipts from Roche/Alexis/ENZO. The group is funded by a large number of smaller grants, as well as a major national grant from the ANR, and it is involvement in the Labex MEDALIS. The group is well connected within the local and national research networks, as well as international collaborators, as many joint publications attest.

Notoriety and drawing power:

The pioneering expertise accumulated by this group also has resulted in many highly productive international and intercontinental collaborations whose results have been published in journals with a great impact. The team leaders are invited to give talks at national and international meetings, mostly of a specialized nature, as well at international universities where collaborators reside. The team has successfully continued to maintain its leadership status and reputation in the field, thanks to these strategic national and international collaborations. The team is also invited to join international funding networks, though a recent one (for a Marie Curie Initial Training Network) was not funded despite scoring well above 90%. Laudable is also the continued interaction and collaboration with previous team members, such as the two publications in Cell Metabolism, as well as review publications.

Assessment of the strategy and 5-year project:

The future plans of the team represent solid, interesting, and achievable goals that emerge fully from the current activities with PARP1, PARP2, PARP3, PARP9 and PARG. Considering the effort that went into making the genetically engineered animals for many of these factors, as well as the open questions in the field, this is sensible. Continuing research with several outside collaborators will continue to strengthen the projects through additional, in part interdisciplinary expertise (such as imaging, replications stress and heterochromatin replication). The projects will also include proteomic approaches (for example studying the PARG interactome), as well as chemical biology approaches, such as the collaboration on PARP3, as part of the MEDALIS consortium. Considering the additional management roles of the group, this path appears focused and wise. The new ventures in chemical biology may appear risky. However, since the group is obviously highly successful in local and international collaborations, and can take advantage of great expertise locally and in the upper Rhine region, the group is encouraged to establish cellular reporter assays, as well as providing the knockouts animals, for their PARP/PARG proteins.

Conclusion:

The team continues its leading global role in the dissection of PARP signaling, in particular with reference to cellular and physiological work using knockout mice. It has accumulated excellent expertise in the field, and has reached out to a variety of exciting and very well published collaborations.

Strengths and opportunities:

- Team with outstanding expertise in PARP biology and signaling.
- Initiates and attracts interesting collaborations locally, nationally and internationally.
- Working toward chemical biology and screening for PARP signaling interference.

Weaknesses and risks:

- Some of the most high impact papers are published with non-local experts, potentially suggesting that the team could benefit from increasing the recruitment of excellent students/postdocs .
- The group has many obtained grants, but most are relatively modest. Strong roles in large international networks, from which the team would clearly benefit from, are currently missing.

Recommendation:

- Considering the pioneering role of the team and continued excellent standing in the field, as well as the successful transition of the group over the last few years, the team is encouraged to take leadership also of major, international funding networks (e.g. European Commission, HFSP).
- Increase presence at international meetings of a broader nature.
- Commission reviews in journals with a broad and high impact.
- Develop the chemical biology platform through excellent local and regional/transborder collaborations
- Develop in-house collaborations.

Team 2: Oncoprotéines

Team leader: Mr Gilles TRAVE & Ms Murielle MASSON

Workforce

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	3	3	3
N2: EPST or EPIC researchers	3	4	4
N3: Other professors and researchers	/	/	/
N4: Engineers, technicians and administrative staff * on a permanent position	/	/	
N5: Engineers, technicians and administrative staff * on a non-permanent position	/		
N6: Postdoctoral students having spent at least 12 months in the unit	3		
N7: Doctoral students	3		
N8: PhD defended	5		
N9: Number of Habilitations to Direct Research (HDR) defended	/		
N10: People habilitated to direct research or similar	3	5	
TOTAL N1 to N7	12	7	7

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the [01/01/2007-06/30/2011] period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d evaluation.

• Detailed assessments

Scientific quality and production:

The team has set out to provide structural information for the main oncoproteins of carcinogenic human papillomaviruses in order to understand oncogenic mechanisms and develop novel therapeutics, which are urgently needed. Team leaders gained with no doubt international visibility in this field of research. They actually got a NIH research grant for extramural research, which is a major accomplishment. Overall, they have several important grants, which make this laboratory very well financed.

Continuing and expanding on the major breakthrough observation published in Mol. Cell in 2006, the team has now published a structure between the C-terminus of 16E6 and the PDZ domain of MAGI1. More importantly, two structures of full-length E6 proteins together with target proteins were resolved. These observations are not yet published but have been presented at the international ICGEB DNA Tumour Virus Meeting in Trieste 2011. It is to be expected that these findings have a major impact on the international papillomavirus research. In addition, the team has used structural information of E6 to develop a dominant-negative E6 protein, which adds novel aspects to the understanding of E6´s oncogenic behaviour. The team has also begun to develop small animal models for cervical cancer and has preliminary data demonstrating that recombinant adenoviruses suppress tumour growth in vivo. The focus of the team is also now on the major E6 targets p53 and PDZ proteins. This had led to the finding that the p53 core is important for E6-induced degradation, the identification of kinases controlling p53 levels in CxCa cells and a bioinformatics approach to rank cellular PDZ proteins as E6 binding partners.

The notion that a point mutation within E6 can convert this oncogenic protein into a suppressor gene is very interesting and novel. One might even wonder why such finding has not been published in a better ranked scientific journal.

In total the team has published 25 articles in peer-reviewed journals of which 7 have an IF>5 and 2 an IF>25 which is an excellent output. There is a slight imbalance between the number of authorships and the three chairs: One of the team leaders is present on 17/25, a team member is present on 9/25 and the other team leader on 6/25 publications. Regarding the impact factor of the published papers, although this team has not published any study in very high impact journals since their “Molecular Cell” paper 2006, the committee was convinced that 2012 will very much likely be a productive year, based on the solid experimental evidences that were presented.

Generally speaking, the quantity of publications is very good and the conducted research is novel and should be prolonged. The team has a “niche” of originality that has to be consolidated. The seminal Molecular Cell paper published in 2006 was not followed by a similar published paper in a highly ranked journal but it was understood from the talk given by one of the team leaders that studies in very good journals are currently in press or al least in revision. The focus of the team is cervical cancer which affects ~500.000 women each year worldwide and has a major socioeconomic impact as the disease onset is around 40 yrs. Thus, the identification of therapeutics is urgently required.

From a translational point of view, investigating the possibility of using small peptides as inhibitors of E6/E6AP interactions is a difficult type of medicinal chemistry, compared to small molecule inhibitors, but if the team successfully maps the binding region to a few amino acids it might consider making small peptides and then modeling small molecules that have the same inhibitory function. The team has a contract with a biotech company indicating commercial interest in the ongoing research. In total the group acquired ~3.1 million € of external funding which is a very good value. Especially, the allocation of a US NIH R01 grant indicates the unique position of the “oncoproteines” team worldwide.

Notoriety and drawing power:

The team leaders are invited on a regular basis to give talks in national and international conferences and also team members regularly give oral presentations in national and international conferences (Boston 2007, Berlin in 2008, Tromso in 2009,…) indicating good visibility and acceptance in their fields. The team has the ability to recruit PhD students and post-docs from abroad indicating international visibility. Furthermore, a large number of national and international collaborations indicate a strong position in the papillomavirus research field.

The visiting committee assumes that one of the team members is coming from abroad so the team has shown its ability to attract people from outside France. It could however do better though, especially considering the very good funding the team receives.

Strategy and 5-year project:

The long-term goal is the identification of therapeutics for CxCa. Based on structural information on E6/E6AP complexes obtained in the previous period, the team plans to identify small molecule inhibitors by in silico approaches and peptide inhibitors. In a nude mouse model for CxCa, newly identified inhibitors will be tested for anti-tumour activity (Project 1). This will be complemented by resolving additional structures of the viral oncoproteins with cellular ligands (project 2), which should also provide relevant information to be used for a rational drug design. In project 3, the long-standing question in the field will be addressed which and how E6 proteins interact with cellular PDZ domains and the functional consequences thereof. Project 4 extends the finding that the several kinases control the amount of p53 in CxCa cells and that this might be linked to the NFκB pathway, which has not been addressed before and may reveal exciting novel links and putative targets for therapy. As the p53 and NF-kappaB fields are very competitive, this team should consider the possibility of establishing collaborations with other laboratories closely located to Strasbourg. In project 5, interactions between E6 from different HPVs and the ubiquitin proteasome system will be explored by a newly developed protein complementation assay and also by a siRNA screen in an E2F reporter cell line. This project is highly ambitious as E6 fusions may not be functional but if successful, it may result in unexpected exciting results. All projects are highly original and some are high risk (1, 5) whereas n° 2,3,4 are of intermediate risk.

Involvement in training:

The training appears very good.

Members of this team participate in several activities/responsibilities. Perhaps team members would even bring more to the unit in terms of international visibility, publications in prestigious journals, …) by being asked to spend less time for these internal activities.

The team is outstanding and has the technical skills and expertise to solve long-standing questions in the field and transform basic science questions into rational drug design.

Conclusion:

Strengths and opportunities:

- Unique team with outstanding expertise in structure determination of Papillomaviruses proteins

- Sufficient external funding

- Attracts students from abroad

- Development of therapeutic approaches

Weaknesses and risks:

- More sophisticated cell culture and animal models may be required to address biologically and therapeutic questions

- No technical staff

- Drug development may fail despite excellent structural information

Recommendation:

No specific ones, except may be the move to animal models to address more in depth biological and therapeutic questions.

Team 3: Modifications post-traductionnelles et cancérogenèse

Team leader: Mr Bruno CHATTON

Workforce

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	5	4	4
N2: EPST or EPIC researchers	4	4	4
N3: Other professors and researchers	2	4	2
N4: Engineers, technicians and administrative staff * on a permanent position	3,60	3,60	
N5: Engineers, technicians and administrative staff * on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	2		
N7: Doctoral students	4		
N8: PhD defended	8		
N9: Number of Habilitations to Direct Research (HDR) defended	/		
N10: People habilitated to direct research or similar	7	7	
TOTAL N1 to N7	21,60	15,60	10

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the [01/01/2007-06/30/2011] period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Scientific quality and production:

This is a newly formed team made up of three groups with different expertise. The team is currently into two groups. The team has a solid, but not extensive, track record of publications. The team has published 35 articles in the previous period, several of them in good journals (Mol. Microbiol., Nucl. Acids. Res., Mol. Cell. Biol., Mol. Cancer Ther.). However, based on the number of permanent positions (14), the output could be improved in terms of quality and quantity. Moreover, the highest impact research seems to have been carried out with other groups outside the unit and the senior author does not belong to the team. There are four permanent staff who account for the majority of senior author publications. It is difficult from the publications to know the role of the other staff in the research and their leadership role in this team, as most are not senior authors. This is a weakness of this team. The development and use of specific antibodies that are active in living cells is a highly ambitious goal that may create novel tools and possibly therapeutics for biomedical purposes and is planned to be used in the major topics of this team, namely translesional DNA synthesis and the characterisation of the ATF7 transcription factor.

Regarding translational research, the antibody technology is novel and has the potential to help to elucidate biological interactions and functions. However, it has only been tested in a limited way and it too early to determine the breadth of its usefulness, in particular for clinical applications.

Integration into the environment:

It is too early to determine how this team will integrate with other groups. At least, all team members are grouped on one floor, which should help them pull together. However, there was no evidence of collaboration between the two groups in this team.

Notoriety and drawing power:

A sub group of the permanent staff participates in international meetings and presents its work. Apparently, this group also contributes to the majority of publications. The team has a low ratio of postdocs and students and this might indicate a lack of drawing power or lack of funding. Two prizes were awarded in 2007 to team members. It can be inferred from the previous period that international collaborations do exist with Japanese and Argentinian teams, but in the description of the planned work no international (and only one national) collaboration is mentioned.

Governance and life:

There is a concern that the team is split into two groups that do not really interact and the only common theme is the antibody platform.

Strategy and 5-year project:

Two areas are planned to be investigated in the next period. (1) proteins involved during translesional DNA synthesis and their modifications will be characterised by 2D-gel and mass spectrometry approaches with the long-term goal to improve chemotherapy. (2) As ATF2 and ATF7 are involved in tumorigenesis, post-translational modifier kinases and E3 ubiquitin ligases will be identified via siRNA screening and co-IP experiments. In addition, as a technical platform scFVs antibodies will be selected that recognize specifically post-translationally modified proteins involved in both projects. As the antibodies should be active in cells, such antibodies might have potential in addressing basic science questions as well as long-term interest as novel therapeutics. However, this project is very risky as – as the authors pointed it out- currently no standard antibodies have been identified that recognize specifically sumoylated or ubiquitilated forms of proteins. There was some preliminary evidence presented that scFv antibodies recognize branched sumo-modifications but the affinity was low and efforts are underway to increase this affinity by mutational analysis. Apart from technology sharing, it is difficult to see integration between the two groups. There seems to be only technological overlap but no biological synergy. Most of the proposed research is vague and difficult to assess how successful they will be. It is difficult to see what is unique about this team and what unifies the two research themes.

Involvement in training:

The PhD students publish their work as first authors and this is a sign of efficient training. However, as mentioned above, the number of students is low compared to the number of permanent staff.

Conclusions:

The team is very large and heterogeneous with respect to the specific topics addressed.

For such a large group (14 permanent positions), the output and quality of results should be improved.

It is not obvious from the proposal and the publications, aside from the scFvc project, whether synergistic effects between the different groups take place.

Strengths and opportunities:

- The scFVs project is very interesting and has great potential

- Large team that could tackle challenging research

- Commercial interest in antibody /protein production

Weaknesses and risks:

- The publication record of this team is fair with only some permanent staff being productive. It is difficult to assess to which extent, team members who do not publish as senior authors contribute to the team and what leading role they are taking. There is no interaction between the two groups in this team and the only overlap is on the antibody technology platform.

- Antibody project is high-risk

Recommendations:

- The team needs to increase impact of publications and to obtain better funding. The latter would help to recruit postdoctoral fellows and PhD students as this group has a large number of permanent staff but small numbers of postdocs and students. There is also a need to encourage those that are less productive to increase their output.

Team 4: Régulation épigénétique de l'identité cellulaire

Team leader: Mr Michaël WEBER

Workforce

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	/	/	/
N2: EPST or EPIC researchers	1	1	1
N3: Other professors and researchers	/	/	/
N4: Engineers, technicians and administrative staff * on a permanent position	/	/	
N5: Engineers, technicians and administrative staff * on a non-permanent position	/		
N6: Postdoctoral students having spent at least 12 months in the unit	/		
N7: Doctoral students	/		
N8: PhD defended	/		
N9: Number of Habilitations to Direct Research (HDR) defended	/		
N10: People habilitated to direct research or similar	/	1	
TOTAL N1 to N7	1	1	1

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the [01/01/2007-06/30/2011] period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Scientific quality and production:

Team 4 is a newly established team within the unit (end of 2011). The group leader has made highly significant contribution to the epigenetic field by publishing genome-wide maps of methylation patterns in cellular models and the developing mouse embryo during its postdoctoral training (3 papers in Nature Genetics in 2005, 2007 and 2010). His excellent standing as a young scientist in the field can readily be seen in grants and prizes obtained, which include merit-based awards from forward-looking programmes such as Avenir and the Rise1 scheme of the European Union FP7 Network of Excellence "EpiGeneSys". The team leader appears to be on an excellent track to establish himself as a key young player in a very competitive field. Made of only one permanent researcher, this group is bound to grow to maintain this high level of quality and competitivity.

Integration into the environment:

The recruitment of Mr. M. Weber to the ESBS could be greatly beneficial to the strengthening of the department, and of the local capabilities, particularly through synergy with the activities of the IGBMC and of the mouse clinic. However, this aspect is not yet highly developed due to the recent arrival of the team in the unit. A specific attention should be paid to develop interactions with other teams (team 1 in particular), since some of the external collaborative projects are pertaining to projects developed within the unit (DNMTs, epithelial-mesemchymal transition). Such strong, local collaborations should be implemented during the next 5-year contract. The group leader has successfully applied to several EU or French grants, securing financing of current research until 2015. Other applications are pending.

Notoriety and drawing power:

As a newly established researcher, the group leader has demonstrated its ability to network efficiently and to get funding. He is recognized as a promising researcher.

Strategy and 5-year project:

The main aspect of the research program is essentially a follow-up of the past project on DNA methylation and early embryogenesis. This is a very timely topic. There are 4 identified projects, with 3 additional potential projects. It is likely that prioritization will be necessary according to available manpower and funding, but all are in principle in line with the current interest of the group. What is however lacking in this report is a strategy for this group to maintain its leadership in terms of access to sequencing technologies and bioinformatics analysis, as well as to animal facilities. As noted for group 1, the "inter-team" connection seems obvious upon reading of the project from a scientific point of view, but does not yet seem to be concrete.

Conclusion:

Strengths and opportunities:

- This is a high profile research group with demonstrated ability to publish high-ranking papers.

Recommendation:

- A particular attention should be paid to reinforce the technical staff, which is one of the objectives of the director, and to prioritize research projects by growing the team in an appropriate manner.

Team 5: RCPG, douleur et inflammation

Team leader: Mr Frédéric SIMONIN

Workforce

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	/	/	/
N2: EPST or EPIC researchers	6	5	5
N3: Other professors and researchers	2	2	2
N4: Engineers, technicians and administrative staff * on a permanent position	2	2	
N5: Engineers, technicians and administrative staff * on a non-permanent position	4		
N6: Postdoctoral students having spent at least 12 months in the unit	5		
N7: Doctoral students	5		
N8: PhD defended	6		
N9: Number of Habilitations to Direct Research (HDR) defended	2		
N10: People habilitated to direct research or similar	5	6	
TOTAL N1 to N7	24	9	7

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the [01/01/2007-06/30/2011] period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Scientific quality and production:

Team 5 results from the fusion of three teams in 2010. The three founding teams have strong expertise in G protein-coupled receptor (GPCR): in molecular biology, protein design and purification, cell biology, molecular pharmacology and animal behavior. In particularly they are investigating GPCRs involved in pain and inflammation. The research topics are multiple, clearly important and consequently highly competitive. They include: the role of RF-aide receptors in both opioïd- and chronic pain-induced hyperalgesia; microglial chemokine receptors in persistent pain; implication of "GASP" sorting proteins in the context of chronic GPCR stimulation and pain. In addition, the team conducts structural and functional studies on purified GPCRs and interacting partners. The team's proposed project benefits from the very strong environment, resources and visibility in the field of drug discovery that exist in the Strasbourg area. If successful, the studies may have significant impact in both basic science and human health.

Studies have been carried out on the adaptative response to chronic stimulation of GPCRs and their consequences on pain/analgesia. A novel family of GPCR-interacting proteins GASP has been identified and seems to play a role in chronic stimulation of various GPCRs. A role for neuropeptide FF receptors (NPFFR) in analgesic tolerance and dependence has also been evidenced following the identification of a selective antagonist for this receptor.

Studies devoted to molecular pharmacology and dynamics of GPCR have been productive and of good quality. Several GPCRs have been used as models in order to study: allosteric modulation (NK2R), ligand binding mechanisms in living cells (M1-R), roles of chemokines in inflammation (CCR5-R, CXCR4-R) and dynamics of β-arrestin interaction regulating NPY-R trafficking.

The third theme dealt with structural and functional studies of purified GPCRs. Studies done on this theme were mainly technological, trying to develop "generic" production and purification methods that would apply to most GPCRs thereby facilitating biophysical and crystallographic studies of this class of receptors. The activities reported on this topic, despite leading to a number of publications and participation to EC-funded programs, failed to deliver strong structural or functional insight on GPCRs. In the same time, the field has substantially moved forward, culminating with the elucidation of 3D structures of several non-rhodopsin GPCRs. The positioning of this theme with respect to international competition and the overall expected impact are less favourable than for the other two themes.

Collectively, the members of this recomposed team have published 44 original articles since 2007, although some senior members of the team provided a moderate contribution in the overall output (2 of the 7 staff scientists were weak producers over the last 5 years). The 7 permanent staff scientists identified in the activity report contributed to 32 peer-reviewed publications since 2007. Team members were in leadership position (first and/or last authors) in 16 of these publications. The quality of the articles is good (mean IF of 5) but outstanding or very good publications are missing. The group has filed 2 patents and has two marketed biotechnological compounds.

The work of this group has a number of potential translational aspects, such as producing tools to study chronic pain but also identifying druggable targets to help the development of compounds that inhibit tolerance to opiates. As GPCRs are seen by many as one of the most druggable family of proteins, this team has the potential to massively contribute to the translational research of this unit. The team has 1 license with a company.

Integration into the environment:

The team is a founding member of the Medalis Labex, which has the objective of developing new drugs. They have obtained an impressive amount of both academic and industrial grants (including industrial PhD fellowships) and are involved in multiple national or European networks. Globally the projects appear more than sufficiently funded. Overall the industrial connection is quite remarkable and still does not prevent the team to be involved in multiple academic collaborative studies. Finally the reorganization of the team based on the recommendations of the previous AERES visit is successful.

Notoriety and drawing power:

Testifying of the visibility of the team are several invited lectures in international conferences (ie: 9), invited reviews (Pharmacol. Ther., Curr. Opin. Pharmacol., Drug discovery today, M/S), the coordination of collaborative projects (ANR, IP FP6, Interreg), industrial contracts with large pharmaceutical companies and biotechs (BioXtal, Domain Therapeutics, Galactis Pharma, Greenpharma, Prestwick Chemicals, Servier, Synthelis...), the attribution of two technological platforms, IMPReSs and TechMedill (integrated in the EU-Openscreen European infrastructure) and the organization of an international meeting on chemokines (Strasbourg 2009). These successes counterbalance the relatively low number of post-doctoral fellows and PhD students for the coming project.

Strategy and 5-year project:

The proposed strategy is clearly the principal weakness of the team project. All four proposed sub-projects are scientifically sound but in quite competitive fields. Based on the current composition of the team it appears quite risky to pursue all the objectives at the same time. Among the senior scientists, 2 will have to support heavy administrative loads, and even with the support of strong technological platforms and of the numerous collaborations, it is not clear how all the studies proposed in project could be carried-out timely in the context of the international competition. In particular, as proposed, the structural studies on purified GPCRs do not appear to stand up to the current competition.

Conclusion:

Good team with clear opportunity for further improvement in both basic science or translational research. The reorganization of the team is in agreement with the recommendations of the previous AERES visit.

Strengths and opportunities:

- Multiple collaborations and connections with both academic groups and companies; integration in a promising well funded Labex.

- Large panel of experimental approaches supported by strong technological platforms

- Interesting and open research projects with potential benefits for health.

Weaknesses and risks:

- Quality of the production (both in basic and translational science) is below what could be expected, based on the available funding and environment; this can lead to progressively waning attraction for young scientists, and to difficulties for grant renewal.

Recommendations:

- This team has rather well performed, but should improve its focus by reducing the number of projects undertaken. Indeed, there is an apparent discrepancy between the proposed objectives and the current human resources. A special effort should also be made to increase the visibility of academic research by publishing larger and deeper articles in more visible journals.

Team 6: RCPG et cardiobiologie

Team leader: Ms Canan NEBIGIL-DESAUBRY

Workforce

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	/	/	/
N2: EPST or EPIC researchers	1	1	1
N3: Other professors and researchers	1	2	/
N4: Engineers, technicians and administrative staff * on a permanent position	/	1	
N5: Engineers, technicians and administrative staff * on a non-permanent position	/		
N6: Postdoctoral students having spent at least 12 months in the unit	3		
N7: Doctoral students	3		
N8: PhD defended	2		
N9: Number of Habilitations to Direct Research (HDR) defended	/		
N10: People habilitated to direct research or similar	1	1	
TOTAL N1 to N7	8	4	1

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the [01/01/2007-06/30/2011] period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Scientific quality and production:

The team investigates the role of recently identified hormones, prokineticins, and their cognate receptors, PKRs, in the differentiation of endogenous stem cells in the heart and kidney. These studies arise from the pioneering observation made by the team leader that PKRs play an important role in the differenciation of heart and kidney progenitor cells. The team arises from a previous ATIP group (2005-2009) and the PI has been acknowledged by several prizes. Although, during the last 5-year period, the articles of the team were published in less-prestigeous journals (IF 5-8), compared to the previous period, the level of the scientific production is still good to very good (n=11, 7 of them being in leadership position), particularly if one considers that the PI is the only permanent scientist of the team otherwise composed of PhD students and post-docs.

This research has a strong translational component and is involving close collaborations with medicinal chemists and clinicians. In this context, 4 patents have been filed (cardioprotection, differentiation of cardiac cells). There are a number of opportunities to translate their research particularly for PKR1 agonists, which require optimization.

Integration into the environment:

The team ia a founding partner of the Labex Medalis and is well funded for the 3-4 years to come (Labex, ANR, FRM total amount around 500 k€).

Notoriety and drawing power:

This relatively recent team has already gained a solid reputation, as shown by prizes to the PI and to students as well as by multiple invited lectures, international meetings and review articles. The ratio of 3 post-docs and 3 PhD students per scientist is the highest in the UMR and pretty unusual in the French context. The PI coordinates 3 funded collaborative studies.

Strategy and 5-year project:

The 5-year project comprises 3 main objectives: i) the determination of how PKR1 signaling in endothelial cells and epicardin-positive progenitor cells (EPPC) contributes heart and kidney functions; ii) the characterization of the role of PKR1 on activation of EPPC derived from heart and kidney in vivo and in vitro; iii) the development of a small non-peptidic molecule that targets PKR1 to activate EPPC in heart and kidney with the objective to repair damaged heart and kidney tissues. Although the PI clearly has the intellectual and technical capacity of managing and developing these topics at the same time, this appears a difficult challenge with the current staff and despite the multiple collaborations. Although the addition of a team member and the recruitment of an assistant engineer is planned in 2013, yet this might not be sufficient to successfully address in parallel the 3 main objectives.

Conclusion:

Good, potentially very-good, team provided it is rapidly reinforced

Strengths and opportunities:

- Interesting and innovative research topics with, in addition, high potential for translational science

Weaknesses and risks:

- The lack of critical mass might jeopardize the team's ability to sustain sufficient impact, productivity and valorisation in a very competitive area.

Recommendations:

- Increase the size of the group.

- At this stage, purely translational aspects appear less urgent than reaching higher academic success.

- Interactions/collaborations between team 5 and team 6, both studying GPCRs, look weak and should be reinforced.

Team 7: Transport membranaire bactérien

Team leader: Ms Isabelle SCHALK

Workforce

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	1	1	1
N2: EPST or EPIC researchers	2	2	2
N3: Other professors and researchers	2	1	1
N4: Engineers, technicians and administrative staff * on a permanent position	3	3	
N5: Engineers, technicians and administrative staff * on a non-permanent position	/		
N6: Postdoctoral students having spent at least 12 months in the unit	2		
N7: Doctoral students	4		
N8: PhD defended	4		
N9: Number of Habilitations to Direct Research (HDR) defended	/		
N10: People habilitated to direct research or similar	3	3	
TOTAL N1 to N7	14	7	4

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the [01/01/2007-06/30/2011] period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Scientific quality and production:

The team leader has assembled a very productive team of researchers who have an impressive output. The team leader is one of the World's most respected experts on iron uptake by the opportunistic "super-bug" P. aeruginosa, and her publication record reflects this. In the period 2007-mid 2011, the team leader published 23 original research articles in some of good quality journals (including JBC, Biochemistry, Env. Micro, Mol. Micro and J. Bact) as well as some of equally highly-regarded but more specialist journals (Bioorg Med Chem, Biometals etc). The team has a good continuous productivity as exemplified by the more recently published 5-6 papers (again, in good quality journals). In brief, the team leader has made a substantial contribution to our understanding of siderophore production and iron uptake. It should be noted that, iron homeostasis is likely to be a (if not "the") key Achilles heel of P. aeruginosa and will doubtless form the mainstay of many future intervention strategies, so the team leader work is of international strategic importance.

The team is of average size for the unit and currently comprises 14 people. These include one postdoc four PhD students, two senior scientists - one assistant professor and one full time researcher at the CNRS and three technicians. A key strength of the team leader's approach is the seamless combination of traditional molecular microbiological and biochemical approaches with the power provided by organic and analytical chemistry. This rare combination of skills is to be encouraged and appreciated and should be further built upon by the Unit. This multidisciplinary approach has already provided the team leader with a number of useful resources e.g., the fluorescence tools that her team relies upon so much.

The team leader's main contribution in recent years has been the detailed characterization of the mechanism(s) involved in the release and re-uptake of the siderophore, [ferri-]pyoverdine, by P. aeruginosa. The future looks set to be even more productive, with the discovery of additional gene products likely to play an important role in this process. The FpvCDEF/FpvGHJK stories look especially interesting, and the team leader has (quite rightly) already formulated some fascinating hypotheses to test there. This is work that offers exceptional promise: if these ideas pan out, the team leader should be also aiming to publish ocassional papers in the very high impact international journals.

Integration into the environment:

As pointed out by the team leader, the team could be reinforced by the presence within the unit of another team working on similar microbial problems (ideally, a group working on bacterial membrane transport, or, better still, microbial signalling). There seems to be plenty of interaction going on, but not so much within the Unit itself as the major interactions rather seem to be with researchers outside the unit.

Notoriety and drawing power:

The team leader has further proven her scientific credentials by attracting external research funding, totalling ca. EU550K, with an additional EU150K ongoing at the start of the evaluation period. This is a very good sign. Now that the team and its leader are well established, in the longer term, the team leader might want to aim higher; instead of accruing a large number of smaller grants.

The team leader has an international reputation and accordingly has the ability to attract international scientists. However, at present, and based on the documentation supplied, most of the students and post docs that have been recruited recently have been "home-grown" French nationals, so this is an area that can be improved.

The team leader has a large number of very successful collaborations with other teams worldwide – another good sign – that have resulted in numerous joint publications. Clearly, several teams are willing to collaborate with the group, and the international connections are in place – perhaps they just need to be strengthened in order to attract more overseas applicants to the laboratory ?

The team leader has presented her work on numerous occasions at international meetings and is clearly deeply involved with the national networks. The team leader resumé lists several relevant and significant "markers of esteem" (membership of various professional bodies, grant organisations etc).

Strategy and 5-year project:

The long-term projects for the whole team, as described by the team leader, look fine overall, although as pointed out below, one of the projects needs refining (if only in its aims and objectives). The PI's project #1 is World-class "blue skies" science aimed at evaluating the structure and function of newly-discovered pyoverdine uptake/recycling elements encoded by the fpv gene clusters. The FpvC story looks especially interesting – very original finding and likely to yield high-value insights. The technology to be employed is a mixture of tried-and-tested molecular microbiology and biochemistry (making mutants, characterizing these, fluorescence imaging, protein purification and in vitro assays etc) combined with newer, state-of-the-art fluorescence approaches such as single molecule FRAP. The plans for investigating the pyochelin pathway are a little more vague and need further elaboration. The risk of failure for project 1 is low, and the probability of success is high.

Project #2 is equally interesting. Though this group is not the first to attempt disruption of iron metabolism/uptake as a therapeutic goal or to apply a "Trojan horse" approach towards uptake of xenobiotics such as antibiotics, the committee believes that with their existing skills combination, they are well-placed to do this. However, although TonB is fully justified as a target, no preliminary data are supplied to suggest that either approach will work – these data would have been useful to bolster the case for support at this stage. Also, many others have previously waded into this territory and failed to come up with anything useful. The risk of "failure" (in the sense of deriving anything that is going to see real translation) of project #2 is therefore high, although there is no doubt that some useful biochemical tools and a better understanding of the system might come out of this. Since this is also the case for any drug discovery project, this should not be seen as a negative comment. It's a classic case of high risk, high reward, and with a probable intellectual payoff whatever the outcome.

Project #3 is another interesting one, predicated around the idea of using P. aeruginosa iron scavenging systems to promote solubilisation (increased bioavailability) of iron from mineralized sources. The introduction was good, and there may be something truly interesting with the pyocyanin/pyoverdine link, although one might wonder "why doing this" and what are the possible economic benefits that might come if this project reaches a translation phase. The idea of retro-mineralization is a nice one, but the description of the proposed work could have been clearer and more specific in its aims and objectives. There is no doubt that this project will deliver data but the project would benefit to be better structured. However, the project leader is new to the laboratory and her project material may take time to bed itself into the existing themes, so these comments should be viewed in that light.

Conclusion:

Strengths and opportunities:

- The team is excellent and is run by an internationally-recognized researcher who has an excellent publication record and a proven record of attracting external funding.

Weaknesses and risks:

- Projects such as #3 (and, to an extent, also project #2) are sidelines that divert away from the more productive areas of research into more speculative or lower priority areas.

Recommendation:

- The team leader should focus the team energies on its core strengths – the analysis, using the tools of molecular microbiology, protein chemistry and organic chemistry, of pyoverdine production/uptake by P. aeruginosa. Thus, the team leader should try to maintain focus on those areas that are established core strengths of the group.

- Now that the group is established, the next steps should aim for (occasional) publication in the very highest rank journals and to attract longer-term large grants.

5 • Grading

Once the visits for the 2011-2012 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).

This score (A+, A, B, C) concerned each of the four criteria defined by the AERES and was given along with an overall assessment.

With respect to this score, the research unit concerned by this report (and, when necessary, its in-house teams) received the overall assessment and the following grades:

❖ Overall assessment of the unit :

Biotechnologie et Signalisation Cellulaire

Unité dont la production, le rayonnement, l'organisation, l'animation et le projet sont très bons.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A	A	A	A

❖ Overall assessment of the team : **GALZI-CHATTON**

Équipe dont la production et le projet sont bons mais pourraient être améliorés. Le rayonnement est très bon.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
B	A	-	B

❖ Overall assessment of the team : **GALZI-DANTZER-SCHREIBER**

Équipe dont la production, le rayonnement et le projet sont très bons.

Grading table:

C1 Scientific quality and production.	**C2** Reputation and drawing power, integration into the environment.	**C3** Laboratory life and governance.	**C4** Strategy and scientific project.
A	A	-	A

❖ Overall assessment of the team : **GALZI-NEBIGIL-DESAUBRY**

Équipe dont la production, le rayonnement et le projet sont très bons.

Grading table:

C1 Scientific quality and production.	**C2** Reputation and drawing power, integration into the environment.	**C3** Laboratory life and governance.	**C4** Strategy and scientific project.
A	A	-	A

❖ Overall assessment of the team : **GALZI-SCHALK**

Équipe dont la production, le rayonnement et le projet sont très bons.

Grading table:

C1 Scientific quality and production.	**C2** Reputation and drawing power, integration into the environment.	**C3** Laboratory life and governance.	**C4** Strategy and scientific project.
A	A	-	A

❖ Overall assessment of the team : **GALZI-SIMONIN**

Équipe dont la production, le rayonnement et le projet sont très bons.

Grading table:

C1	C2	C3	C4
Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A	A	-	A

❖ Overall assessment of the team : **GALZI-TRAVE-MASSON**

Équipe dont la production et le rayonnement sont très bons. Le projet est excellent.

Grading table:

C1	C2	C3	C4
Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A	A	-	A+

❖ Overall assessment of the team : **GALZI-WEBER**

Équipe dont la production est excellente. Le rayonnement et le projet sont très bons.

Grading table:

C1	C2	C3	C4
Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A+	A	-	A

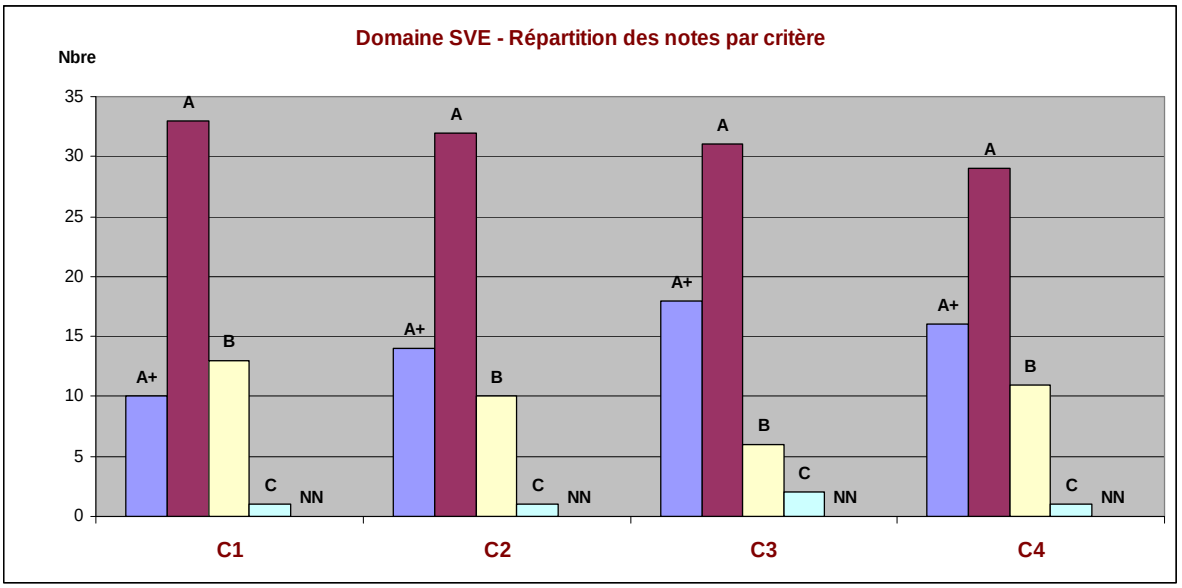
6 ● Statistics per field : SVE au 10/05/2012

Notes

Critères	C2	C2	C3	C4
	Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A+	10	14	18	16
A	33	32	31	29
B	13	10	6	11
C	1	1	2	1
Non noté	-	-	-	-

Pourcentages

Critères	C1	C2	C3	C4
	Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A+	18%	25%	32%	28%
A	58%	56%	54%	51%
B	23%	18%	11%	19%
C	2%	2%	4%	2%
Non noté	-	-	-	-



7 • Supervising bodies' general comments

UNIVERSITÉ DE STRASBOURG

Monsieur Pierre GLORIEUX
Directeur de la Section des Unités
AGENCE D'EVALUATION DE LA RECHERCHE ET DE L'ENSEIGNEMENT SUPERIEUR (AERES)
20 rue Vivienne
75002 PARIS

Alain BERETZ
Président

Strasbourg, le 28 février 2012

Objet : Rapport d'évaluation de l'UMR 7242 (réf. S2PUR130004548)
Réf. : AB/EW/N° 2012-81

Direction de la Recherche

Affaire suivie par
Eric WESTHOF
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Cher collègue,

Je vous remercie pour l'évaluation de l'unité de recherche «Biotechnologie et Signalisation Cellulaire» (BSC – UMR 7242) dirigée par Monsieur Jean-Muc Galzi.

Vous trouverez ci-joint les réponses du directeur d'unité de recherche concernant les erreurs factuelles et les remarques et appréciations du comité d'experts.

Les points à améliorer seront discutés avec le directeur d'unité dans un esprit constructif pour l'avenir de la recherche à l'université.

Je vous prie d'agréer, Cher Collègue, l'expression de mes sentiments distingués.

Alain BERETZ
Président

P.J. :

- **Une première partie corrigeant les erreurs factuelles**
- **Une seconde partie comprenant les observations de portée générale**

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Jean-Luc GALZI
Directeur

Pr. Eric WESTHOF
Vice-Président Recherche
Université de Strasbourg

Illkirch 27 February 2011

Object: Observations regarding the evaluation of the UMR 7242 by the AERES in 2012

Laboratoire de
Biotechnologie et
Signalisation cellulaire

UMR 7242

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Dear President,

We welcomed the AERES evaluation committee on January 24, 2012 for a one-day visit to our laboratory.

All members of the laboratory wish to thank the members of the committee for their objective expert analysis of our past and future research, teaching and technology-transfer activities.

We were impressed by the level of scientific expertise of the members of this highly international committee.

We all appreciated the carefully documented and detailed report made for the unit as a whole, as well as for each individual team, and express our general agreement on the conclusions and recommendations of the experts.

As we are invited to comment about statements of facts and to make general observations, we would like to highlight the following points:

General observations:

- *Contribution of professors to research activities*: In the French university system, professors and assistant professors have a heavy teaching duty that represents nearly 50% of their workload. This situation is in marked contrast with that in other European countries and accounts for reduced basic research commitment. As such, the members of team 2 who “should be asked to spend less time in these activities” cannot really bring more to the unit. Along the same line, the activity of the personnel from team 3 cannot be simply estimated at its arithmetic value. There are 4 professors and 2 university technicians and engineers who spend 50% of their time in teaching activities. One may regret such differences between teaching and non-teaching scientists.

- *Team fusions*: Teams 3 and 5 both result from recent fusion of three independent teams with respectively 2- and 1-year common research activities in each new team. In each case, the number of research topics was drastically reduced and common projects have been shaped. Some of the projects mentioned in the printed documents delivered during fall 2011 were, for instance, no longer prioritized at the time of the committee visit. Although the members of both teams agree with the committee that there is still room for improvement as suggested, they also wish to emphasize that common experience is required to build the cohesion of a team, a process that takes time.

In conclusion, all comments made by the committee are well taken and we shall consider the recommendations to further improve the quality of our scientific production in the coming years.

On behalf of the UMR 7242 members,
Jean Luc Galzi