Laboratoire de biophotonique et pharmacologie

Rapport Hcéres

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

Research Units Department

AERES report on unit:

Laboratoire de Biophotonique et Pharmacologie

LBP

Under the supervision of the following institutions and research bodies:

Université de Strasbourg

CNRS

December 2011

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:	Laboratoire de Biophotonique et Pharmacologie
Acronym of unit:	LBP
Label requested:	UMR
Present no.:	7213
Name of Director (2009-2012):	Mr Yves MÉLY
Name of project leader (2013-2017):	Mr Yves MÉLY

Members of the committee of experts

Chair:	Ms Catherine ROYER, Montpellier
Experts:	Ms Francine ACHER, Paris (représentant CoNRS)
	Mr Yves ENGELBORGHS, Leuven, Belgium
	Mr Olivier FERON, Bruxelles, Belgium
	Mr Urs RUEGG, Geneva, Switzerland
	Mr Daniel SCHERMAN, Paris (représentant CoNRS)
	Mr Bernhard WEHRLE-HALLER, Geneva, Switzerland

Representatives present during the visit

Scientific Delegate representing AERES:

Mr Yves GAUDIN

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

Ms Marie-Hélène METZ BOUTIGUE (Université de Strasbourg)

Ms Florence NOBLE (CNRS)

Report

1 • Introduction

Date and conduct of visit: December 5 2011

The visit took place on December 5th, 2011. An international team of 7 scientists, with expertise in the research areas of the 3 teams of the LBP, conducted it. The visit started with a general presentation of the history of the LBP 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 post-docs, the technical staff and the staff scientists. The committee questioned the CNRS and UdS 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 management team 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 location of the unit, and overall description of its field and activities:

The laboratory for Biophotonics and Pharmacology at the School of Pharmacy of the University of Strasbourg was created in 2009 by the CNRS. It evolved from a Department called the Department of Physical Chemistry and Pharmacology, which was one of the 6 Departments of the Institut Gilbert Laustriat. In 2008 this unit was closed and 4 new UMR were created, including the LBP on January 1, 2009. The LBP is an interdisciplinary laboratory, from biology, applying approaches from physics and chemistry, to biomedical questions including retroviral infections, cancer and cardiovascular disease. The unit is rather large, with approximately 56 permanent staff projected for January 1, 2013.

Management team:

The director, Yves MÉLY (PRCE1), is currently assisted by J. de MEY (PR1), K. TAKEDA (DR1-CNRS) and V. SCHINI-KERTH (PR1), the other three team leaders. The proposed unit will be directed by Yves MÉLY, who is also responsible for team 1, and he will be assisted by M. DONTENWILL (DR2-CNRS) and V. SCHINI-KERTH (PR1), who will lead the other two teams.

Unit workforce:

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	28	24$ *(31*)*	20 (**)
N2: EPST or EPIC researchers	14	15	13 (**)
N3: Other professors and researchers	4	4$	3 (**)
N4: Engineers, technicians and administrative staff *****on a permanent position	11.8	13#	
N5: Engineers, technicians and administrative staff ***** on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	18		
N7: Doctoral students	23		
N8: PhD defended	31		
N9: Number of Habilitations to Direct Research (HDR) defended	3		
N10: People habilitated to direct research or similar	27	23	
TOTAL N1 to N7	**99.8**	**56 *(63*)***	**36 (**)**

(*) *The numbers in brackets* assume that all professors and assistant professors retiring in 2011 and 2012 will be replaced in 2012 and onwards. This has been agreed to by the council of the Faculty and does not include any new creation of positions but only replacements.

(**) These apparently lower numbers result from the large number of retirements in 2011 and 2012 in the unit, and do not take into account the programmed replacement. The total number of non producers (N1 to N3) in the LBP is actually only 4 and will drop to 2 in 2013.

(#) Note that 4.8 positions (2007-11) and 5 positions (2013-17) of engineers and techniciens are dedicated to LBP platforms, informatics and administration. These positions will thus not appear in the tables for the teams given below.

($) Takes into account the shift of an "AHU" from the N4 to the N1 category in 2012

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

****** Number of producers in the 2008-2011 period who will be present in 2013-2017. 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 LBP represents a laboratory in which the local and national supporting organisations (Université de Strasbourg - UdS and CNRS) have heavily invested, both in scientific personnel and in other support, indicating that from their standpoint, the LBP represents a sound investment for the future. The scientific production is of overall good quality and the level of publication of the Unit is good, although not equally distributed among the teams. The laboratory attracts a large number of PhD students, in particular from outside of France, although attracting the best students from UdS, capable of obtaining a university research stipend has proven difficult. Moreover, there are few postdoctoral associates. The unit has obtained a significant level of financial support via contracts with the private sector (pharmaceutical, biotech and food industry) and national granting agencies. In contrast, European and international funding and involvement remain rather modest. Despite the strong scientific activity performed in the unit, the overall orientations and goals of the unit project do not appear particularly integrated between teams, although an increase in inter-team collaborations has occurred since 2009. Greater use of the state of the art fluorescence microscopy methods developed by team 1 in the studies carried out in the cell biology based teams will allow for higher impact science for the entire unit.

Strengths and opportunities:

The unit appears to be undergoing a strong positive evolution, with increasing productivity, increasing funding, increasingly important research results, and increasing international attractiveness. Further faculty and researcher retirements in the coming years represent further opportunities for recruitment of strong young researchers who can attract more international funding and recognition.

Weaknesses and risks:

The technical support in the laboratory is very limited; particularly from the university, given the large number of faculty and research staff. A significant increase of its international competitiveness hinges on strengthening such technical support. Despite the solid competence of the participants, funding for fluorescence instrumentation development will be difficult to obtain, given the positioning of this group at the national and international level in optical imaging. The international visibility of the unit remains modest, despite the high quality and competence of the researchers, and must be increased.

Recommendations:

Concentrate resources, both financial and human, on the most promising projects.

Work to better position the unit in the national and European landscape.

Move toward a more aggressive publishing policy, based on prioritizing research goals to the most significant problems.

3 • Detailed assessments

Assessment of scientific quality and production:

The scientific contributions of the three teams are quite distinct. Team one is recognized for developments in fluorescence methodologies and for the application of these methods to understanding the molecular basis for HIV replication and assembly. Team two is involved in cell signalling and cancer, and their most important scientific contributions involve understanding the molecular basis for the control of receptor internalization, the role of FAK phosphorylation in cell migration, and the role of integrins and their partners in tumorogenesis. This represents a promising niche in an otherwise very competitive field. Team 3 has centred its work and project on natural products, in particular polyphenols, and their role in the regulation of endothelial signal transduction pathways, and liver disease and cancer. This team also has excellent recognition and expertise in cardiovascular physiopathology.

The unit overall has a very sound level of research productivity. The large majority of faculty and research staff published multiple papers in the last period. The majority of their publications have appeared in well-respected international journals, albeit specialty publications, with IF in the range of 3-7. These include JMB, JBC, Biophys. J., Biochemistry, JOC, J. Phys Chem, J Cell Sci, Langmuir, J Med Chem, Mol. Pharm., PLoS One, Endocrino, BBA, Cardiovasc. Res., and about 1-2 articles per year overall published in the next level, very high quality journals with IF of 7-15. In the last review period, the number of articles published in this next tier of journals, more general and of higher impact, increased significantly. Studies were published in NAR, JACS, Angew. Chem., Nano Lett, Biomaterials, Faseb J, Mol Biol Cell, Oncogene.

The trends in the bibliometry of the unit are difficult to assess, given the broad based scientific activities of the different teams. Overall the quantity and quality of the publications is on the rise, with a total of 260 publications over the period of assessment, and a 20% increase in the last 3 years. While the impact of the work of team 1 appears to be increasing, that of teams 2-3 appears less dynamic when considering only the articles coming principally from the work of these teams

Assessment of the unit's integration into its environment:

The unit has been quite successful in attracting outside funding, nearly 0.85 M€ per year in recent years from both the public and private sector, up quite a bit from the prior assessment period, although this is a general trend in France, given the reorganization of research. Integration of the group at the local level is quite good, but its integration into European programs remains rather modest. Unit members are also involved in University governance (the president for example) and administration.

Assessment of the research unit's reputation and drawing power:

The LBP members are recognized in their community and many of them participate in the governance of national and international societies or journal editorial boards. A young researcher was awarded a Bronze medal by the CNRS. Most of the scientists have been invited to speak at key international conferences in their field. Hence, the level of international recognition may be improving. Indeed the institute is involved in a large number of international collaborations. The LBP attracts international students and postdocs, however not from the top international groups in the respective fields.

Assessment of the unit's governance and life:

The organisation of the unit into three teams with a limited number of research topics (although a little bit broadly spread), and a clearly identified direction team appears to function appropriately. It is unclear why the unit has trouble getting Ph.D. research stipends from UdS, although since all teams belong to the same Graduate School, this can be a limiting factor. The annual internal call for collaborative projects between teams in the Unit is a good unifying factor.

Assessment of the strategy and 5-year project:

In the next period, the unit proposes 3 teams in the fields of HIV, cancer and cardiovascular disease, respectively, each concentrating on two research areas. This project involves, for the most part a continuation of ongoing themes, although somewhat refocused. Taken independently, each of the team's projects presents at least one strong research area. However, overall, and given the broad spectrum of interests of the different teams, the research strategy does not appear to be sufficiently developed to enhance significantly the cohesion of the Unit. Moreover, the proposed interactions between the teams appear rather superficial such that it is not clear that the quality of the biological and biomedical scientific projects would benefit significantly from interdisciplinary interactions between the teams. Although a few joint publications have appeared there would be great benefit to forge stronger more profound collaborations, in particular more implementation of team 1 techniques in team 2 and 3 problems. The positioning of team 1 on the national and international level is not in line with the high quality and competence of the team. In addition to very solid instrumentation abilities, the team boasts unique strengths in probe development that should be more visible. In teams 2 and 3, the subprojects are not of equal significance and feasibility.

Assessment of the unit's involvement in training:

With a significant number of research staff (including the unit director) being on the faculty of UdS, the unit is very involved in teaching and training. However, they are not able to attract the top Masters students in their field at UdS. In part, this is because these students do not have the background necessary for the physical and organic chemistry/instrumentation based activities of team 1. In part this is due to the strong competition by other units in the area. The unit members are involved in 3 different masters programs and in University organization. Significantly, they are not involved in any Masters programs at the physics-chemistry-biology interface.

4 • Team-by-team analysis

Team 1: Biophotonics of molecular and cellular interactions

Team leader: Mr Yves MÉLY

Workforce

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	9	9$ *(12*)*	6 (**)
N2: EPST or EPIC researchers	3	4	3 (**)
N3: Other professors and researchers	2	2$	1 (**)
N4: Engineers, technicians and administrative staff * on a permanent position	2	2	
N5: Engineers, technicians and administrative staff * on a non-permanent position			
N6: Postdoctoral students having spent at least 12 months in the unit	7		
N7: Doctoral students	9		
N8: PhD defended	14		
N9: Number of Habilitations to Direct Research (HDR) defended	3		
N10: People habilitated to direct research or similar	9	8	
TOTAL N1 to N7	**32**	**17 *(20*)***	**10 (**)**

(*) *The numbers in brackets* assume that all professors and assistant professors retiring in 2011 and 2012 will be replaced in 2012 and onwards. This has been agreed to by the council of the Faculty and does not include any new creation of positions but only replacements.

(**) These apparently lower numbers result from the retirements in 2011 and 2012 in Team 1.

($) Takes into account the shift of J. Godet (AHU) from the N4 to the N1 category in 2012.

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

** Number of producers in the 2008-2011 period who will be present in 2013-2017. Criteria: http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

The work of team 1 is concentrated in two areas, development of fluorescence methodologies and their applications in the field of HIV research. In the first area, their most original contribution has been the development of new fluorescent probes and caged compounds. Their competence in setting up advanced microscopy instrumentation (2 photon FCS, FRET/FLIM, and recently super-resolution microscopy) is also a strong asset of the team. For the second axis of research, the most significant contribution of the team has been in identifying the role of protein oligomerization and molecular dynamics during viral particle formation and retro-transcription.

While the team clearly has the competence to implement state of the art fluorescence methodology, in fact they have done so over the years, most of the past highly recognized work has been in spectroscopy, less in live cell microscopy. In the field of retroviral research, while the *in vitro* studies of molecular mechanisms are interesting, the most promising work appears to be in their quantitative biophysics studies in live cells, using the sophisticated optical microscopy methods implemented in their group.

Team 1 is highly productive, with an increase in the impact of their published work over the last assessment period. Team 1 has the largest number of publications of the three teams (125 publications among which half coming directly from their work), as well as the largest number of high impact publications. Moreover, in the last few years these latter appear to be increasing. Publications from the team include articles in respected journals such as JACS (2), Angew. Chem. (1), Nanoletters (3), Nucleic Acid research (4), J. Biol. Chem (1), Biophysical J. (3), J. Virol (1) and Retrovirology (2). Their production also includes two patents, one of which (a kit for detection and quantification of apoptosis) has been licensed.

Assessment of the research team's integration into its environment:

The team is well integrated into UdS, although more University-based student stipends should be forthcoming. They are able to attract a reasonable level of funding through one HFSP grant (350 k€), 6 ANR grants (903 k€), 4 ANRS grants (259 k€) and smaller grants from Sidaction, Sanofi Pasteur, OSEO and FRM that have allowed a good level of productivity. The relationship between the development projects of the team and very similar ones at a nearby institute is unclear. This team has the only European contract of the unit.

Assessment of the research team's reputation and drawing power:

The team boasts a CNRS Bronze Medal and a Dr Honoris Causa. The team leader and other members have been often invited to speak at international meetings (42 invitations), serve on governing bodies of international scientific societies or editorial boards. Their involvement in research review on the national or international level has been rather limited (little membership in national institutional governing or strategic bodies, peer review committees such as AERES, ANR, or European review panels). The team attracts many foreign students (Eastern Europe and developing nations), but fewer post-docs. While the team leader is well-known and respected internationally in the fluorescence community, international recognition in fluorescence microscopy/cell biology is less apparent. The committee regrets that this team is not part of the EuroBioImaging, or French BioImaging infrastructure.

Assessment of the strategy and 5-year project:

The stated main objective of Team 1 is to further upgrade and develop its leading edge instrumentation STED, PALM/STORM) and fluorescent markers and apply these to the HIV-1 nucleocapsid field. They have identified new partners of HIV1 Ncp7, and they plan to investigate the relevance and the function of these interactions in HIV infection. The high resolution fluorescence approaches and dye developments should be key to this effort.

What is clear is that the team has the competence and knowledge to become an important player in the field of quantitative microscopy. It brings the novelty of new probe development that other groups in the country do not have. However, it is unclear how the team will bring such positive points to bear on the projects of the other teams in the unit, and in the surrounding institutes. In particular, the project involves acquisition of about 0.8 M€ in state of the art equipment. Securing the funding for these efforts, in the actual national context will be a challenge and may not be simple. In the field of HIV, the number of specific aims in the project is quite high and it is likely that the most profound and significant advances will be made in the live cell quantitative microscopy areas.

Conclusion:

- *Overall opinion on the team:*

This is a very good team, with high productivity. They are open to collaborations and diffusing their know-how. The team is highly interdisciplinary (physics, chemistry and biology), as attested by the diversity of journals in which they publish.

- *Strengths and opportunities:*

- Strong experience and competence in fluorescent probe development and in 2-photon and super-resolution microscopy.
- High level equipment, homebuilt –with all its flexibility- , that they fully master.
- The association of these technologies with the field of HIV allows direct application of these promising techniques in an important field.

- *Weaknesses and risks:*

- The cost of developing and maintaining their equipment is quite high and national recognition (i.e., IBiSA) would be important to ensure continued success.
- They have a modest level of technical assistance for the maintenance of the machines.
- Also they will be losing competence in synthetic organic chemistry with one retirement and one transfer in 2013.
- The HIV work is focussed almost uniquely on Ncp7 interactions, which are important, but perhaps not the most significant aspect of the problem

- *Recommendations:*

- They need to increase their recognition and impact in fluorescence imaging approaches, since it is the main focus of their developmental projects.
- For the HIV theme, microscopy applications are likely to provide the most significant results, such that focusing more strongly on these goals is advised, and perhaps extension beyond Ncp7 would be wise.

Team 2: Tumoral signalling and therapeutic targets

Team leaders: Ms Monique DONTENWILL

Workforce

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	7	6 *(7*)*	6 (**)
N2: EPST or EPIC researchers	8	9	8 (**)
N3: Other professors and researchers	1	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	6		
N8: PhD defended	9		
N9: Number of Habilitations to Direct Research (HDR) defended			
N10: People habilitated to direct research or similar	10	10	
TOTAL N1 to N7	**27**	**19** ***(20*)***	**15 (**)**

(*) *The numbers in brackets* assume that all professors and assistant professors retiring in 2011 and 2012 will be replaced in 2012 and onwards. This has been agreed to by the council of the Faculty and does not include any new creation of positions but only replacements.
(**) These apparently lower numbers result from the retirements in 2011 and 2012 in Team 2.

***** **If** different, indicate corresponding FTEs in brackets.
****** Number of producers in the 2008-2011 period who will be present in 2013-2017. Criteria: http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

Research has been conducted on three different aspects, involving (i) $\alpha 5\beta 1$ integrin inhibition by small molecules and expression analysis in glioblastoma model, (ii) dynamic analysis of FAK localization using quantitative fluorescence microscopy in function of FAT domain regulation by tyrosine phosphorylation, and (iii) analysis of intracellular transport of neuropeptide Y receptor and signaling through CD47 and PDE4.

The team has made some important contributions in the first research topic such as the demonstration of $\alpha 5\beta 1$ as a relevant target in glioblastoma and the correlation between expression level and tumour aggressiveness. The demonstration that a small non-peptide inhibitor can be a successful strategy is also of note

As concerns the second theme of the team, quantitative analysis of FAK dynamics has been pioneered by this group. They have demonstrated changes in dynamic localization to either focal adhesions or membrane ruffles as a function of src regulation and Tyr 925 phosphorylation. They have also identified the FAK interface with dynein driven microtubule reorientation during cell polarization and revealed the FAK/paxillin interface as a new therapeutic target.

Most of the results of the team (64 articles among which only 29 directly from their work) have been published in recognized specialized journals. Only a few of the publications directly from the team appeared in higher impact journals [Traffic –IF 5.57- (1), Cell Mol Life Science –IF 6.61- (2) Br. J. Pharmacol –IF 4,71- (3), Glia –IF 5.54- (1)]. Impact of publications could be increased particularly when one considers the size of the team: 5 professors and assistant professors, 8 researchers.

One patent was filed for the use of adenine in the treatment of lupus.

Assessment of the research team's integration into its environment:

The research has potential for medical and socioeconomic impact. It is not surprising therefore, that external funding comes essentially from cancer related agencies (the national foundations (Ligue (5), l'ARC (1), INCA(2)), and the team has been reasonably successful in this aspect. In addition to their contracts with these agencies, the team members are involved in the Canceropole GrandEst.

Assessment of the research team's reputation and drawing power:

The committee notes adequate recognition by the international community for one senior research fellow. The team has a relatively limited implication in peer review, excepting a few instances from the leaders of the sub-teams. They have relatively few international collaborations (many in Strasbourg and France), albeit with pertinent groups in the field.

Assessment of the strategy and 5-year project:

The research project is the result of a reduction (and focusing) to two research axes, implicating studies aimed at further identification of biological functions of $\alpha 5\beta 1$ and FAK to better define or identify pathways and potential therapeutic targets. The plan also includes focusing on screening of new integrin specific inhibitors with new nucleotide-based libraries (new innovative approach) in addition to phage display and small molecules.

The project involving the focal adhesion kinase is an interesting and promising fundamental project in cell biology, that will likely lead to important new insights into the molecular mechanisms of the associated transduction pathways. Their interactions using the technologies of team 1 are also quite promising.

Moving towards applications, screening is a risk but relevant for pharmacological approach to this question. The effort does not bring up very original questions but uses state of the art screening test. There is some potential to produce patentable structures. Screening of natural compounds is potentially interesting but suffers from low specificity and multiple, as yet undefined targets in a given cell.

Conclusion:

- *Overall opinion on the team:*

This team has limited productivity and international recognition but is going through a transitional period. Important recent findings related to the interplay between p53 and integrins, and the characterization of new FAK partners are however promising. An important effort is necessary to translate the ambitious new projects aiming to dissect integrin and FAK signaling into high-standard research validated by good publications and patents.

Although the projects of both groups are of high biological relevance, their scientific output has been rather limited for their size, especially regarding sub-team 1. Involvement of both groups in lead compound identification is appreciated.

- *Strengths and opportunities:*

- One of the group leaders is young with new projects only recently emerging and accepted in the field.
- Increasing productivity is expected in this area in the near future. Of note, replacements of 3-4 previously productive scientists, will be an opportunity to develop approaches and methodology and to increase output.
- The project has potential for finding new cancer related drugs (targeting both integrins and FAK).

- *Weaknesses and risks:*

- This team has two distinct projects, one of which (FAK) is significantly more molecular than the other, which remains primarily descriptive.
- The true internal productivity of this team is modest.
- Strong international competition will require increased aggressiveness in publishing strategies.
- No functional model exists for testing role of integrin or FAK in mechanosensing.
- Given the long road from identification of lead compound to product, funding from public sources may be limiting, and the team will have to redouble its efforts for private agency funding.

- *Recommendations:*

- It is recommended for the two main areas, to focus on good cell biology and imaging analysis.
- As mentioned above, the project has potential for finding new cancer related drugs. This will not be simple for several reasons including the complexity of the biological system, the fact that the targets are not completely identified for the two projects and the fact that the underlying biology is not yet understood. Therefore, focusing on molecular mechanisms will be important to the translational work.
- More pertinant structure-function analysis is needed to identify screening approaches (biological read-out as well as fluorescence based).

Team 3: Experimental pharmacology, physiopathology and therapeutics

Team leader: Ms Valérie SCHINI-KERTH

Workforce

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	12	9 *(12*)*	8 (**)
N2: EPST or EPIC researchers	3	2	2 (**)
N3: Other professors and researchers	1	1	1
N4: Engineers, technicians and administrative staff * on a permanent position	2	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	9		
N7: Doctoral students	8		
N8: PhD defended	8		
N9: Number of Habilitations to Direct Research (HDR) defended			
N10: People habilitated to direct research or similar	8	5	
TOTAL N1 to N7	**36**	**15 *(18*)***	**11 (**)**

(*) *The numbers in brackets* assume that all professors and assistant professors retiring in 2011 and 2012 will be replaced in 2012 and onwards. This has been agreed to by the council of the Faculty and does not include any new creation of positions but only replacements.
(**) These apparently lower numbers result from the retirements in 2011 and 2012 in Team 3.

* **If** different, indicate corresponding FTEs in brackets.
** Number of producers in the 2008-2011 period who will be present in 2013-2017. Criteria: http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

The research of this team is divided in 2 axes (previously 3). One concerns protective effects of polyphenols in various diseases in which oxidative stress is involved and effect of polyphenols on endothelial formation of NO and other vasodilators. The second axis deals with various signalling pathways essential for vessel wall integrity. The first project in the polyphenol field remains highly descriptive, although it is popular in public health. However, we note a tendency towards a more molecular approach, especially with the recent recruitment of a chemist-engineer.

The second project in cardiovascular pathophysiology uses various original transgenic models to elucidate the molecular basis of signal transduction in a particular area of atherosclerosis formation and vascular calcification. This is a long term, ambitious project with promise to deliver important insights.

Overall the team has a high level of good quality publications (59 articles among which 37 directly from their work) in multidisciplinary journals [JBC (2), Plos ONE (2), FASEB J (1)] and in well-respected journals in their field [Gastroentero –IF 12.5– (1), Pharmacol. Ther. –IF 9.5- (1), Mol. Interv –IF 7.5- (1), Atherioscl. Thromb. Vasc. Biol. –IF 7.5- (1), Oncogene –IF 7- (1), Cardiovasc. Res. –IF 6- (1), Am. J. Pathol. –IF 6- (1)]

Two patents have also been obtained.

Assessment of the research team's integration into its environment:

The team has several important contracts, mostly applied funding sources for the first theme and more fundamental science sources for the second (ANR physiol -180 k€-, ANR PCD -238 k€-, ANR Blanc -608 k€-) of several hundred thousand euros to support their projects. In particular, the subject of polyphenols in human health is acknowledged by the general public, and this has lead to some non-traditional funding possibilities for this project.

Assessment of the research team's reputation and drawing power:

The team leader is a member of international committees and has given several conferences in international meetings but she seems to be the only team member with such a visibility together with the leader of the second project, although the team is made up of 15 permanent scientists (professors and researchers).

Assessment of the strategy and 5-year project:

The group proposes to investigate the cellular penetration of polyphenols, their localization and molecular targets. They will thus prepare polyphenols linked to a fluorophore. This will 1) require to select some specific polyphenols (not indicated) 2) assume that the fluorophore will not modify the properties. This approach may be questionable. There are some doubts on characterizing a pharmacophore mediating vasorelaxation based on polyphenols. A molecular approach was missing in the research presented for the 2007-2011 period and it is not clear whether the group chose a promising approach in their new project. Investigating the cellular transport of polyphenols, which is a critical point for a possible therapeutic use, is of interest but bioavailability and metabolism are also important issues. It was not clear what are the key questions that need to be addressed according to the community. Altogether the group will continue developing the same approaches so that the risks are limited.

The second group uses the up to date technology such as cell type specific knock-outs to decipher the molecular mechanisms implicated in atherosclerotic plaque formation. The research revolves around the Wnt5 signaling pathway and the cross-talk with the PPAR¤ transcription factor. The complex interplay has begun to be deciphered by this group, and further progress appears imminent, although the links of some aspects of the project to the pathology appears a bit tenuous. This risk-taking approach is nonetheless clear and promising.

Conclusion:

- *Overall opinion on the team:*

- This is an experienced team however stretched between two separate themes, with one of them scientifically more defined at a mechanistic level and thus more promising.

- *Strengths and opportunities:*

- The team has a recognized competence and large collection of experimental models in vascular function and a unique expertise in vascular physiopathology.

- *Weaknesses and risks:*

- Although research of both groups focuses on cardiovascular pathologies, the coherence between the two groups is not obvious and should be strengthened.

- *Recommendations:*

- For the first group, the elucidation of molecular mechanisms of action of the most interesting compounds should be the prioritized (if possible), as was stressed by the former evaluation.
- Major innovation is needed in the long-standing endothelium-polyphenol field; otherwise the competence of this large team could also prove to be useful in other domains of vascular pathology and pharmacology.
- The second group theme investigating the transduction in vascular pathophysiology could benefit from the team's extended competence.

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 « Laboratoire de Biophotonique et Pharmacologie LBP » :

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 1 "Biophotonics of molecular and cellular interactions" (MELY-MELY):

Excellente équipe à tous points de vue.

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 2 "Tumoral signalling and therapeutic targets" (MELY-Dontenwill):

Équipe dont la production, le rayonnement et le projet sont bons, mais pourraient être améliorés.

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	B	-	B

Overall assessment of the team 3 “Experimental pharmacology, physiopathology and therapeutics” (MELY-SCHINI-KERTH) :

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

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	B	-	A

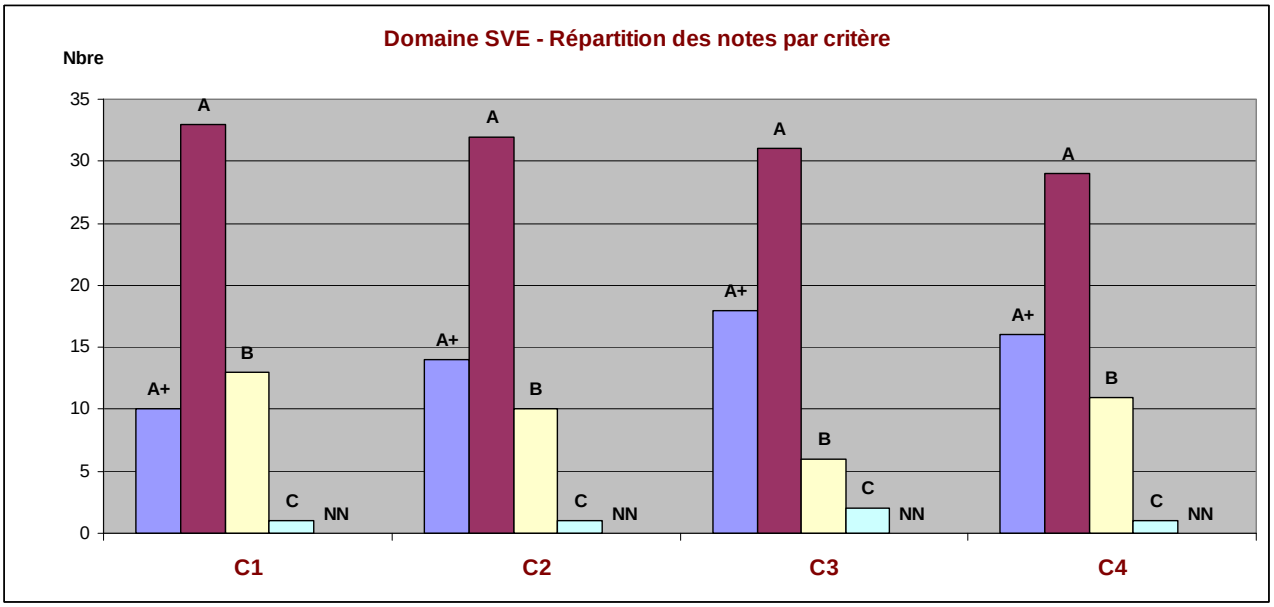
6 • Statistics per field

Notes

Critères	C1	C2	C3	C4
	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Gouvernance et vie du laboratoire	Stratégie et projet scientifique
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
	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Gouvernance et vie du laboratoire	Stratégie et projet scientifique
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 de recherche
Agence d'évaluation de la recherche et de l'enseignement supérieur (AERES)
20 rue Vivienne
75002 PARIS

Alain BERETZ
Président

Strasbourg, le 2 mars 2012

Objet : Rapport d'évaluation de l'UMR 7213 Laboratoire de biophotonique et pharmacologie (réf. S2PUR130004514-RT)
Réf. : AB/EW/N° 2012- 90

Affaire suivie par
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Direction de la recherche

Cher collègue,

Je vous remercie pour l'évaluation de l'unité mixte de recherche « Laboratoire de biophotonique et pharmacologie » (UMR 7213) dirigée par Monsieur Yves Mély.

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.

Je n'ai pas de remarque particulière à ajouter au nom de l'Université.

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

Alain BERETZ

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P.J. :

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

Laboratoire
de Biophotonique
et Pharmacologie

CNRS UMR 7213

Directeur : Yves MELY

Illkirch, le 27 février 2012

Members of the AERES committee and to whom may be concerned

Yves Mély
Profeseur

Objet : Response to the AERES evaluation

The laboratory of Biophotonics and Pharmacology would like to thank the members of the committee for their work and involvement in the evaluation of our laboratory. We are very pleased that the committee acknowledged the good quality and level of publications of the Unit, as well as its strong positive evolution, with increasing productivity, increased funding, increasingly important research results and increasing international attractiveness.
We would like also to thank the committee for their comments and suggestions. We will integrate most of these suggestions in our future strategy to increase the excellence of the laboratory.

Comments on the assessment of the Unit.

1. In their overall opinion, the experts stressed the need to further integrate the overall orientations and goals of the unit project, through a greater use by the cell biology teams of the state of the art fluorescence microscopy methods developed by team 1. We would like to highlight that a large part of these new techniques, namely single molecule spectroscopy, PALM, STED and the AFM/fluorescence microscopy combination have only been developed during the three last years, so that inter-team collaborative projects using these instruments have just started. Moreover, as the committee mentioned, the inter-team collaborations had already markedly increased since 2009, and this tendency will further grow in the next years.
2. Within the weaknesses, the experts raised a concern about the possible difficulty to obtain funding in fluorescence instrumentation development, due to the international positioning in optical imaging of the team involved in this development. We would like to stress that the shift of this team from the purely molecular to the cellular field has only started in 2006, explaining why applications of the optical imaging techniques are quite recent. Moreover, within the last years, this team raised each year sufficient funding (ANR, FP6, ANRS, ARC…) to achieve all the planned developments, so that we are quite confident for the future plans.
3. The experts recommend to concentrate resources, both financial and human on the most promising projects. We would like to emphasize that we have already made significant efforts to optimally concentrate our research efforts, by having only three teams and in total, only six research axes for a Unit with close to 60 permanent staff.

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4. The experts recommend to better position the unit in the national and European landscape and move toward a more aggressive publishing policy. As the committee underlines in their general comments as well as in their comments for the teams, the unit shows a strong positive evolution, with an increasing number of publications in high IF journals within the last few years (Nature Structural Biology, Gastroenterolgy, JACS, Nucleic Acid Res, Angew Chem, Nano Lett, Faseb J…). Moreover, members of the unit have got national and international recognition through i) a CNRS bronze medal, ii) nomination as Doctor Honoris Causa, editor or editorial board member of journals, Chair and Vice-Chair of international committees, iii) organization of international conferences and iv) invitations to reference congresses…

5. The experts stressed the difficulty of the laboratory in getting PhD stipends from UdS. In fact, this difficulty exists for many laboratories in Strasbourg, due to the very high competition in the biological sciences Doctoral School. Nevertheless, team 2 was quite successful, having got 5 PhD research stipends from UdS, during the five last years. In contrast, due to its activities the interface between biophysics/chemistry/biology, it proves difficult for team 1 students in chemistry or physics to get these PhD stipends in a competition where all questions from the jury are related to biology.

6. The assessment of the strategy and 5-year project stating that the research strategy does not appear sufficiently developed to enhance the cohesion of the Unit and that the proposed interactions appear rather superficial, appears rather severe. As underlined in our project, the developed microscopy techniques are the unifying link and the asset of the Unit. A large part of the projects of team 2 and team 3, as well as the biological projects of team 1, rely on the use of these techniques. The use by teams 2 and 3 of the techniques and probes developed by team 1 is clearly described in the written research project and appears much more developed than it was in the past.

7. In the same paragraph, the committee underlines that the positioning of team 1 on the national and international level is not in line with the high quality and competence of the team. In fact, the team has already a strong and still increasing recognition in the fluorescence field (organization of a MAF meeting, Chair of the MAF permanent committee, most productive French scientist in the field, high recognition and productivity in ratiometric probes, CNRS bronze medal for a work based on fluorescence probes) and in the field of the HIV nucleocapsid protein (invitation to all international meetings on this protein, most productive scientist in the field, strengthening of the team by J.L. Darlix, a world expert in the field, 2nd most highly cited paper in the field). As mentioned above, the recognition in optical imaging, a quite recent topic in the team, could still be improved, but already the PI has been invited within the last 3 years to 8 national and international workshops and conferences (Boston, San Francisco, Kiev, Saarbrucken, Wroclaw…) on advanced imaging techniques.

8. In the assessment of the unit's involvement in training, the committee mentioned that the Unit is not involved in any master program at the physics-chemistry-biology interface. This is not fully true since we are heading the molecular and cellular imaging master, that is at the physics/biology interface. Note, that to our knowledge, no masters fully at the interface of the three domains exist in Strasbourg.

Comments on the assessment of team 1

We are pleased that the committee recognized the high quality and productivity of the team, as well as its strong interdisciplinary character.

1. The experts mentioned in their assessment of the team's integration into its environment that the relationship between the projects developed by the team and those of a nearby Institute (IGBMC) are not clear. In fact, the objectives of team 1 and the IGBMC are quite different. The optical imaging platform of the IGBMC is mainly equipped with commercial instruments, while team 1 develops its own instruments.

IGBMC is highly interested in the expertise of team 1 in FLIM, and high-resolution optical microscopy. Recently, the IGBMC and team 1 applied together for an Equipex project, where the tasks of team 1 were related to developments in STED and its coupling with FLIM. Moreover, team 1 has an increasing number of collaborations with various teams in IGBMC (D. Moras, M. Ruff, N. Rochel, P. Schultz, J. Cavarelli), further showing that the relationships between the two are developing and based on complementary expertise.

2. In their assessment of the team's reputation, the committee indicated that the team is moderately involved in national institutional governing and strategic bodies, peer review committees such as AERES, ANR, or European review panels. This could be largely explained by the fact that about 2/3 of the team members are less than 41 years old. Moreover, it should be mentioned that the PI is member of the National council of the University (85th section), and member of the CoNRS (30th section). He was also involved in two AERES visits and has been reviewer for many ANR projects. Moreover, another team member is in the board of GFPP and has been in the scientific committee of ANRS.

3. In the assessment of the strategy, the experts mentioned that it is unclear how the team will bring their instrumental and probe developments to bear on the projects of other teams and in the surrounding institutes. This remark is surprising since the interaction with the other teams is already validated through a number of common papers and is well described in the written project of the application for the renewal of the laboratory. Similarly, collaborations with teams in surrounding institutes is already validated through the numerous collaborative published papers using these developments, as for instance with IBMP (M. Heinlein and C. Ritzenthaler), IGBMC (N. Rochel, D. Moras), IBMC (S. Muller), ECPM (R. Ziessel), ICS (C. Marques), CAMB (A. Wagner), ESBS (J.L. Galzi, B. Ilien)… The experts also mentioned the possible difficulty to raise the budget (0.8 M€) for the further development in the equipment. In fact, the mentioned budget was planned in the frame of the Equipex project, for which we have got unfortunately a negative answer. Nevertheless, the instrumental platform is currently fully operative, and sufficient for 90% of the planned projects. For the remaining 10%, only part of the planned budget will be sufficient to achieve our main goals, and should be obtained through applications to various sources (ANR, European projects, University…), where we successfully applied in the past years. Moreover, since the platform (PIQ) in which the developed instruments are included, is now fully operative, we also plan for applying for an IBISA label, which should provide us additional budget.

4. Concerning the weaknesses and risks, we agree that the level of technical assistance is modest. We plan to apply for an additional position (BIATOSS) to the University. To compensate the decrease in the number of chemists (one retirement and one transfer), we will present in 2013, one candidate for a CR recruitment in CNRS. Moreover, we would like to stress that we will keep a strong expertise in organic chemistry with the CR1 CNRS (Bronze medal CNRS) and the chemist PhD students still present in the team. Finally, it is true that we largely focus our HIV projects on NCp7, which is a key protein in HIV. The main reason is that this protein is highly conserved and constitutes, thus an extremely interesting target for anti-HIV therapy. Moreover, on a fundamental point of view, the interactions of this protein with host proteins are still poorly defined, and need to be investigated to find new clues for antiviral therapies. Finally, as mentioned in the project, integrase and Tat will also be investigated in relationship to NCp7.

5. The recommendations are fully in line with our planned strategy and will thus be naturally followed.

Comments on the assessment of team 2

We agree that our productivity should be improved (increased number of publications, especially in journals having higher IF) - this will be a major goal for the upcoming period. However, we wish to respond to some statements concerning our productivity. With an internal productivity (arising directly from the team) of 29 publications (with 65% of IF > 4), the productivity of team 2 is close to that of team 3 (37 publications,

with 70% of IF > 4). Thus, there are no large differences between teams 2 and 3 in terms of numbers of publications, % of internal publications and % of internal publications of IF >4. We regret that our publications in Mol Cell Biol (IF 5.95), BBA Mol Cell Res (IF 5.02), Int J Cancer (2 papers - IF 4.74), and Cell Signal (2 papers – IF 4.24) were not recognized by the committee. We also regret that the committee has made no remarks concerning our published work on NPY receptors, CD47 and cyclic nucleotide phosphodiesterases.

It should be noted that the 3 research axes during the current evaluation period are dissimilar: numbers of researchers involved differ and some projects are much younger than others. This is particularly true for the “integrin” subteam that emerged starting in 2005 and has functioned with only 2 researchers until the end of 2010. Effort was concentrated on setting up useful networks between biologists and chemists and also between biologists and clinicians with the aim of promoting translational research that did not previously exist. The next period should be more fruitful in terms of publications due to these established collaborations. Similar considerations apply to the “FAK” subteam; in addition, the investment in setting up and supervising the PIQ platform should be taken into account.

Concerning the future project of team 2, our aim is to promote sharing of our respective expertises, so that subteam 1 will benefit from the imaging expertise of subteam 2 and conversely, expertise in translational research from subteam 1 will be proposed to subteam 2. We believe that we have contributed to the identification of alpha5beta1 integrin and FAK as being true targets of therapeutic interest in cancer cell biology. However, we wish to correct certain of the impressions of the committee concerning our involvement in “screening”. In collaboration with D. Rognan, we proposed an original concept: target a new druggable binding pocket on the integrin instead of the classical RGD binding site. The in silico screening done by D. Rognan produced promising compounds, 3 out of 60 are currently being tested in depth by subteam 1 in pertinent cancer-related functional assays. We hope to obtain patents in the near future. A clear mechanistic understanding of alpha5beta1 integrin function and signalling that we focus upon is requisite for evaluation of such compounds. Concerning FAK, we consider that our strategy to target interactions between FAK and its partners (notably paxillin, in the FAT domain) to be original as compared to current efforts that target kinase domains. This will require clear molecular understanding of such interactions that will be a focus of subteam 2. Altogether, our attempts to obtain and characterize new pharmacological tools of potential therapeutic interest are always based on fundamental molecular and cellular studies, and eventually xenograft models in mice. They will represent about 15% of our research activities and will always be done in collaboration with pertinent experts (e.g. in improving SAR or in taking validated lead compounds towards product; development of medium throughput assays will done on the screening platform at the ESBS directed by Pascal Villa).
Lastly, in support of the activities of team 3, we will characterize the effects of a selected few natural compounds (studied and/or synthesized by team 3) using our models and expertise: this is not (large-scale) screening of natural compounds and will represent a small minority of our activities. We would also emphasize that functional models for testing the role of FAK in mechanotransduction are currently developed in the lab. These implicate the use of substrate with variable rigidities combined with AFM and traction-force microscopy.

Comments on the assessment of team 3

Assessment of scientific quality and production:
The first project in the polyphenol field remains highly descriptive, although it is popular in public health. We note a tendency towards a more molecular approach, especially with the recent recruitment of a chemist-engineer.
Indeed, the major aim of the first project is to unravel the molecular and cellular mechanisms underlying the vasoprotective and anti-cancer properties of polyphenol-

rich natural sources, which have been consistently observed in numerous epidemiological studies, and also in experimental and clinical studies. Although the beneficial effect of these natural products is unquestionable, little information is currently available regarding the biologically active compounds mostly due to the fact that these natural sources are incredible complex mixtures, which contain several hundreds of different polyphenols. Therefore, this first task is approached with investigations at different levels of complexity: cell level, tissue level, and animal level, and with either a biologically relevant well-defined polyphenolic structure or biologically active complex mixtures of polyphenols such as those found in some natural products. Cell experiments with a well-defined polyphenol will help us to decipher the molecular events mediating the stimulatory effect of the polyphenol leading to cellular responses. Such mechanistic approaches will greatly benefit from the recent recruitment of a chemist-engineer, who will provide unique polyphenolic tools to better understand the structure-activity relationship, and also from the microscopy competence of team 1. Investigations of isolated tissues such as blood vessels will help us to evaluate the vasoprotective effect of polyphenols and, in particular, their ability to strongly dilate blood vessels by releasing the vasoprotective factors nitric oxide and endothelium-derived hyperpolarizing factor, and then characterize the underlying mechanism. The *in vivo* investigations will demonstrate that the selected polyphenolic compounds and polyphenol-rich products have indeed vasoprotective and anticancer activity. Although such *in vivo* investigations are mostly descriptive, they provide crucial proofs that these compounds are bioavailable and health benefits in an intact animal. Such investigations are an essential step before moving into translational research.

Assessment of the research team's reputation and drawing power:
International visibility mostly of the team leader and the leader of the second project.
Our team is made up of 15 permanent scientists, including 12 teaching scientists and 3 scientists (2 CR1 and 1 CR2 recruited in 2010). Most of the teaching scientists are heavily involved in administrative work (President of the University of Strasbourg, Head of the Master of Pharmaceutical Sciences, Head of the Master of Pharmacology, Head of a Professional Licence) and teaching (the 5 members involved in teaching pharmacology all contribute to more than 200 teaching hours per year). End of 2010, the newly recruited CR2 member has been invited to give an oral communication at the International Conference on Polyphenols and Health, Barcelona, Spain. In the future, we will continue to contribute activity to communicate our science at both the national and international level, and we are convinced that our young scientists will participate actively.

Assessment of the strategy and 5-year project:
The first group proposes to investigate the cellular penetration of polyphenols.
This point is part of one of the three tasks, which have been proposed in the vascular field (polyphenol-induced activation of endothelial NO synthase, polyphenol and vascular ageing, polyphenols and the hepatopulmonary syndrome) and the two tasks in the cancer field (anticancer properties, antiangiogenic properties of polyphenols). Although polyphenols induce numerous potential protective effects on target cells including endothelial cells and cancer cells, little knowledge exists in the literature regarding the interaction of polyphenols with target cells. Therefore, we propose to determine whether polyphenols can interact with specific cell membrane domains and/or penetrate into cells to elicit cellular responses. The team is well aware that such investigations need to be performed with the most relevant polyphenolic structure (bioavailable active polyphenols) and will benefit from the expertise of Team 1.

Concerning the factual errors:

- Page 2 : In management team paragraph : Yves Mély (PRCE1) instead of PR1
- Page 9: in the weaknesses and risks: substitute "two retirements" by one retirement and one transfer.

Pr Yves Mély