CRBM - Centre de recherche de biochimie macromoleculaire

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on research units and interdisciplinary research units:

Centre de Recherche de Biochimie Macromoléculaire

CRBM

Under the supervision of the following institutions and research bodies:

Centre National de la Recherche Scientifique - CNRS

Nouvelle Université de Montpellier

December 2013

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

Department for the evaluation of research units

On behalf of AERES, pursuant to the Decree of 3 november 2006[1]*,*

- Mr. Didier HOUSSIN, president
- Mr. Pierre GLAUDES, head of the evaluation of research units department

On behalf of the expert committee,

- Mr Marc BILLAUD, chair of the committee

[1] The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n ° 2006-1334 of 3 November 2006, as amended).

Evaluation report

This report is the result of the evaluation by the experts committee, the composition of which is specified below.
The assessments contained herein are the expression of an independent and collegial deliberation of the committee.

Unit name:	Research Center for Macromolecular Biochemistry
Unit acronym:	CRBM
Label requested:	Unité Mixte de Recherche CNRS/UM1-UM2
Present no.:	UMR 5237
Name of Director (2013-2014):	Ms Anne DEBANT
Name of Project Leader (2015-2019):	Ms Anne DEBANT

Expert committee members

Chair:	Mr Marc BILLAUD, CNRS, Institut Albert Bonniot, Grenoble
Experts:	Mr Philippe CHAVRIER, CNRS, Institut Curie, Paris
	Mr Claude COCHET, INSERM, CEA iRTSV/BCI, Grenoble
	Mr Emmanuel GARCION, INSERM, Angers
	Mr Roland LE BORGNE, CNRS, Institut de Génétique et Développement de Rennes
	Mr Emmanuel LEMICHEZ, INSERM, C3M, Nice
	Ms Claudine MAYER, Institut Pasteur, Paris (Representative of CNU)
	Mr Alex MCDOUGALL, CNRS, Observatoire Océanologique de Villefranche-sur-Mer
	Ms Marie-Hélène VERLHAC, Collège de France, Paris (Representative of CoNRS)
	Mr Winfried WEISSENHORN, Université Joseph Fourier, EMBL, Grenoble

Scientific delegate representing the AERES:

Mr Jacques BARATTI

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

Mr Michel DESARMÉNIEN (director of Doctoral school CBS2)

Mr Jean-François FERVEUR, CNRS

Mr Bernard GODELLE, Université Montpellier 2

Mr Jacques MERCIER, Université Montpellier 1

1 • Introduction

History and geographical location of the unit

The Centre de Recherche de Biochimie Macromoléculaire (CRBM) has been created in 1968 as a CNRS unit. Since 2007, the CRMB is a joint research unit (Unité Mixte de Recherche, UMR 5237) supported by the CNRS and both the Universities of Montpellier 1 and Montpellier 2. The CRBM is located on a CNRS campus, route de Mende in Montpellier. This unit was located in an old building dating from the late 60's and the laboratoty moved in december 2010 to a new building with 3814 m^2 of laboratory space. The CRBM shares this building with the Center for the Study of Pathogens and Health Biotechnology (CPBS). Furthermore, the buildings of the CRBM and of the Institute of Molecular Genetics of Montpellier (IGMM) are physically connected. Thus, around 450 scientists work in these three Institutes on biological and biomedical related topics. The vicinity of these laboratories on the same campus has created the conditions of partnerships and fostered collaborations, successful co-participations to grant applications, co-management of core facilities and platforms as well as common maintenance of core services. Of note, an on-going program that aims at gathering all the units working in chemistry in Montpellier (Pôle Balard) is supported by the CNRS, UM1 and UM2. This chemical cluster will be located in an unique building, route de Mende, at a close distance of the CRBM.

Ms Anne DEBANT succeeded to Mr Paul MANGEAT who was the director of CRBM from 2003 to 2010. In January 2011, at the beginning of the former 5-year contract, there were 13 teams at CRBM. During 2011 and 2012, following an international open call in 2009-2010, four new teams settled down in the Institute : one senior team (Mr Patrick LEMAIRE, Programme Incitatif à Mobilité d'Equipe CNRS) and 3 junior teams : Ms Bénédicte DELAVAL (ANR Chaire d'excellence), Mr Dominique HELMLINGER (ATIP/AVENIR) and Mr Dimitris XIRODIMAS (ATIP/AVENIR). Thus, during the 2011-2014 period, the CRBM was organized in 17 independent teams. This report assesses the activities and projects of 15 teams since the team of Mr Pierre CHARNET will leave the CRBM at the end of the contract, i.e. the beginning of 2015 and the teams of Mr Philippe FORT and Mr Pierre ROUX are going to merge in a single team for the forthcoming contract.

Management team

The current director of the CRBM is Ms Anne DEBANT (DR2, CNRS) and she applies for renewal for this 5-year contract. She is in charge of the scientific strategy and she oversees the administrative management of the Institute. She is helped in this mission by a deputy director and an administrative director who runs a department comprising 5 staff members involved in the administrative, financial and human resources organization. These three persons constitute the management board that meets on a weekly basis. The director is also assisted in her strategic decisions by a PI board that includes all the CRBM team leaders and meets once a month. Furthermore, a Scientific Advisory Board (SAB) has been established in March 2013 to review the quality and relevance of research conducted at the CRBM and to prospectively advise the direction on the proposed scientific programs. The Laboratory Council, which is a statutory body, meets 4 times a year and makes suggestions on the purchase of laboratory equipment, on the unit organization and on all administrative matters related to the daily life of the Institute. Finally, team leaders are delegated to common duties, from the organization of the CRBM retreat to the management of animal facilities.

AERES nomenclature

SVE1, LS1, LS2, LS3, LS6

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	24 (23 ETPT)	22 (21 ETPT)
N2: Permanent researchers from Institutions and similar positions	30 (26.5 ETPT)	25 (21.5 ETPT)
N3: Other permanent staff (without research duties)	30 (29 ETPT)	29 (28.2 ETPT)
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	15	14
N6: Other contractual staff (without research duties)	13	10
TOTAL N1 to N6	**112 (106.5 ETPT)**	**100 (94.7 ETPT)**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	27	
Theses defended	32	
Postdoctoral students having spent at least 12 months in the unit	13	
Number of Research Supervisor Qualifications (HDR) taken	5	
Qualified research supervisors (with an HDR) or similar positions	30	25

2 • Overall assessment of the interdisciplinary unit

The committee has been impressed by the scientific policy that was initiated by the former director and that was unflinchingly pursued during this 5-year contract by the current director. The CRBM direction has defined clear objectives to improve the scientific dynamics of the Institute and to reinforce its national and international visibility. The first concrete action consisted in the priority recruitment of new teams. Seven teams that were not present in 2008 are either already integrated in the Institute (4 teams) or are going to be in the frame of the new contract (3 teams). The majority of these teams are led by young investigators who have been hired on permanent positions (CNRS/INSERM/University), attesting to the attractiveness of the CRBM. Second and concomitantly, a reorganization of the pre-existing teams has been undertaken based on an internal evaluation of their scientific achievement. This reshuffling of the teams was also intended to refocus the CRBM on its main domains of expertise. Thus, for the proposed contract, one team (is going to move outside the CRBM and another team is going to merge with the team led by Mr Pierre ROUX. Therefore, the CRBM will be organized into 18 teams in 2015. Furthermore, the establishment of the CRBM in a new building has promoted the opportune conditions for the partnerships with neighboring Institutes (CPBS, IGMM). The committee has also been sensitive to the active involvement of the CRBM and the teams thereof in structuring programs developed in the Nîmes-Montpellier area that have been created to boost research in basic biology, biology of health and translational medicine (such as the Labex Epigenemed, the Computational Biology Institute, the Cancéropole Grand Sud-Ouest, the SIRIC Montpellier Cancer and also the Pôle BioSanté Rabelais).

However, even if the assessment is globally very positive, the committee has identified some frailties in the organization of the CRBM. Firstly, although the committee supports the strategy that aimed at recruiting new teams, care should be taken to provide the appropriate conditions for the favourable development of these 7 teams especially in terms of limited ITA/BIATSS positions. Even senior teams that joined the CRBM during the former contract do not have a technical support staff yet. Secondly, it was not always clear for the committee members what the research priorities are since the CRBM already covers a wide spectrum of biology (from the cell cycle and cytoskeleton dynamics to cancer and evolutionary biology as well as structural bioinformatics). The recent recruitment of excellent scientists working in new fields, although opportunistic, blurs the strategy's focus and weakens the consistency of the CRBM program. This consideration is strategic in terms of visibility if one considers that the domains of investigation of the CRBM are not fundamentally different today from the ones of IGMM or other biological institutes implanted in Montpellier. Finally, as detailed in the Team assessment, circumscribed concerns have been raised on the feasibility and relevance of some team projects that are going to be developed during the forthcoming contract.

Srengths and opportunities related to the context

1. The overall quality of the scientific production of the CRBM is very good to first-rate and the scientific contribution of the majority of the teams is nationally and internationally recognized.
2. Most of the scientific projects is well-thought, addresses original or even cutting-edge questions, is based on skilful teams and supervised by team leaders with a recognized leadership.
3. The recruitment of new teams including young investigators as well as the restructuring of some existing teams have created the conditions for a novel scientific dynamics that demonstrate the international attractiveness of the CRBM (6/18 team leaders are foreigners) and that portends well for the future.
4. The CRBM is well integrated in the scientific and medical networks that have been developed in Montpellier (Labex, Cancérople, SIRIC. Pôle Rabelais, etc.).
5. High quality of the platforms shared by the CRBM with other Institutes in Montpellier (Montpellier RIO Imaging (MRI), Montpellier Genomic collection, animal facility, etc.).
6. The strategy to run common services and platforms as well as to foster scientific collaborations between the 3 Institutes (CRBM, CPBS, IGMM) located on the same campus is consistent.
7. The involvement in the translational research and in the valorisation of research results (30 patents filled, creation of the start-up Splicos) is tangible.
8. The fund raising at a national level, but also at an International level is highly competitive.
9. The commitment of the CRBM teams to teaching is strong.

Weaknesses and threats related to the context

1. There is a lack of clarity in the choice of the main research lines that will constitute the scientific cornerstones of the future CRBM.
2. Although most of the scientific projects are sound and are internationally competitive, some concerns have been raised on the feasibility and appropriateness on some of the 5-year programs.
3. The number of technical positions is limited and that may affect the optimal establishment of recently recruited teams.
4. The committee estimated that the team led by Mr Gilles DIVITA develops a research project that does not proprerly fit in the main research axes of the CRBM in its novel configuration.
5. The reduction of general core funding will require to assume infrastructure expenses.
6. The number of post-docs is limited.

Recommendations

The committee members wish to reimphasize that the restructuring changes of the CRBM that have been initiated by the former director and decisively operated under the direction of the current director deserve to be praised. In its new configuration, the CRBM has been consolidated since the scientific activity is supported by competent teams that are largely internationally competitive and by an ambitious and proactive policy that aimed at recruiting new teams headed by young team leaders. A noticeable effort has also been made to streamline the scientific heterogeneity of the CRBM and to refocus on the main aeras of expertise. Yet, this strategy has not been conclusively pursued and there is still a pressing need to delineate the scientific domains that will constitute the major fields of investigation, knowing that an imprecise strategic vision has a direct impact on the national and international visibility of the Institute. In this context, the committee recommends that the team of Mr Gilles DIVITA prospects lie outside of the CRBM to find an academic structure that provides a synergistic environment. Also, it is important at this stage of the CRBM institutional life to secure the recently integrated teams as well as the 3 teams that are going to arrive soon. The Comittee does not underestimate the difficulty in obtaining ITA/BIATSS positions in the present French research system, but the direction should strive to allocate technical support to these teams in order to strenghten their integration. Finally, discussion of the visiting committee with members of the personal has revealed that the information related to the scientific strategy of the unit, especially with the staff scientists, is not always appropriately transmitted. Thus, an effort should be made to improve the sharing of information between the “PI board” and the rest of the unit.

3 • Detailed assessments

Assessment of scientific quality and outputs

Between 2008-June 2013, the CRBM has published more than 280 articles in peer-reviewed journals (this number is the summation of papers in which the CRBM investigators are the main contributors as well as associated papers). The production has been globally constant along the past 5 years as well as the distribution of the papers according to the IF of the journal in which they are published. More than half of the articles are released in journals with an IF<5. However, the CRBM is at the origin of a few articles published in journal highly-rated journals (Science, Curr Biol, J Cell Biol, EMBO J, Nature comm, Plos Genet). Thus, considering this quantitative information, it appears that the CRBM teams are performing well and have a steady production. However, the strengthening of the CRBM visibility also depends on publication of articles in journals with higher IF and it is expected that the Institute in its new configuration will evolve in this direction.

Assessment of the unit's academic reputation and appeal

The success of the CRBM in recruiting 7 new teams during the past 4 years including 3 teams led by foreign scientists is undeniable evidence of the attractiveness of this Institute. Furthermore, 9 scientists have been hired at CNRS/INSERM and 1 has been recruited on a faculty position during this contract. Heads of the teams and staff members are regularly invited to give seminars at national/international conferences (>120 invitations during the 5-year contract) and they participate also to national and international networks. Several team leaders have been involved in the organization of national and internatioanl meetings and workshops (eg. European Cell cycle confernce, EMBO workshop, Conferences Jacques Monod, a meeting on proteolysis in Spain, Genome annotations jamborees, Grand-Sud Ouest Canceropole meetings). Furthermore, team members are associated editors in several journals (Development, Biology of the Cell, Nucleic Acids Res, Current Opinion in Genetics and Development, Developmental Biology, etc.). CRBM members are implicated in the management of scientific societies (A team leader has been the President of the Société de Biologie Cellulaire de France (SBCF)) and they are also members of various scientific committees (CoNRS, INSERM, ANR, ARC, Canceropole, etc.). Finally, prizes have been awarded to CRBM scientists (Fondation Schlumberger pour l'Education et la Recherche as well as Young Researcher Prize of SBCF, Fondation L'Oréal pour les Femmes et la Science, Cristal du CNRS, Languedoc-Roussillon Chercheurs d'avenir. A senior team leader has been elected EMBO member in 2011. In consideration of these different elements, there is no doubt that the CRBM reputation and appeal are good and that the direction has cleverly capitalized on the attractiveness of the Institute and on the quality of biological sciences in Montpellier to profoundly reorganize the Institute and create the conditions favorable for creating this overall dynamism.

Assessment of the unit's interaction with the social, economic and cultural environment

The CRBM has been fairly successful in terms of research valorization since 35 biomedical patents have been filled during the contract. Some teams of the unit have been committed to translation of their research to the clinic, such as the team that has developped an inhibitor of DOCK5, a Rac1 exchange factor, that prevents bone loss and has a clear therapeutic potential. Other teams have been involved in industrial partnerships with pharmaceutical companies. In addition, one of the team leaders at CRBM, has founded in 2009 with a scientist working at IGMM, a biotechnological startup called Splicos SAS whose activity aims at indentifying chemical compounds that correct faulty alternative RNA splicing events with a view towards clinical applications. In this frame, this team has shown that a novel splicing isoform of the tumor suppressor p53 may constitute a useful biomarker for cancer progression. Finally, scientists working at CRBM punctually participate to large public conferences.

Assessment of the unit's organisation and life

The CRBM has four organizational bodies : a management board, a PI board, a Laboratory Council and the Scientifc Advisory Board (SAB). The first one includes the director, the deputy director, the administrative director and meets once a week to address administrative and budgetary matters. The operational tasks of the PI board that includes the team leaders of the CRBM is concerned with strategic decisions on scientific policy. The Laboratory council is consulted 4 times a year to make propositions on the laboratory equipment (renewal, purchase of novel appliances) and on the organization of the daily life of the Institute. Finally, the SAB which is composed of 4 internationally renowned scientists was created in 2013 and sat once in March to help the direction in preparing the

five-year contract. The SAB's mandate is to advise the direction on the scientific strategies and to provide recommendations on future orientations and means to reinforce the CRBM international recognition. This organizational structuring of the CRBM is globally adapted to its functioning as attested by the forceful changes that have been implemented during the past four years. Yet, there are three points on the governance that ought to be addressed: 1) The missions of the Laboratory Council in the CRBM appear rather limited in scope compared with the administrative attributions of this body which is also entitled to discuss budgetary questions, human resources, policy of contracts as well as all questions dealing with the scientific strategy, 2) During the on-site visit, the staff scientists expressed their wishes to be more tightly associated with the discussions regarding the scientific strategy of the CRBM. One option would be that representatives of the scientists sit in the PIs' board. Alternatively, and more consistently with the official missions of the Laboratory Council and the first point raised, these questions should be openly discussed in order to request their opinions and advices on these matters that impact on the conditions of their research, 3) The direction of the CRBM has not decided to be organized in Departments like many other Institutes of this size. A choice to identify Departments may have helped to define the priviliged research fields that the direction intends to enforce (this question of a lack of a clear definition of the main research lines of the CRBM has already been reviewed above in this evaluation) and also to create the appropriate conditions for scientific exchanges between teams working on related topics.

The total funding of the CRBM is 10 M€ a year (including core funding by the CNRS and UM1/UM2 with salaries included as well as the research grants). 0.6 M€ out of 0.82 M€ of core funding (without salaries) are allocated to infrastructure expenses, an incompressible expense that increases each year. Thus, the direction has a 0.2 M€ fund at its disposal for the CRBM's scientific policies. Consequently, 15% of each grant (the total research grants obtained by the CRMB teams is 2.4 M€) is taken up by the direction to defray the costs for common expenses and to contribute to the Institute policy. These budget figures indicate that the CRBM teams are efficient at securing grants; the amount of financial resources is in the range of CNRS/University Institutes of this size and the allocation of the funds appears appropriate.

Assessment of the unit's involvement in training through research

CRBM staff scientists are committed to supervising graduates and undergraduates students, including foreign students in ERASMUS and ERASMUS Mundus undergraduate programs. 35 students have defended their thesis between 2008 and 2013, and 26 students are currently doing their PhDs, thus indicating the good quality of tutoring of the Institute teams. The majority of the CRBM teams are affiliated to the Life Sciences and Health Doctoral School (CBS2, ED 168) that depends of both UM1 and UM2 and which includes 42 research units, 500 scientists with an HDR and manages 400 PhD students/year. During the on-site visit, the committee met the director of the CBS2 who presented the activity of the Doctoral School and confirmed that the CRBM was an Institute providing satisfactory student guidance. CRBM staff scientists are involved in teaching at UM1 (Nutrition; Health Engineering, EDAMUS, National Diploma of Pharmacy), UM2 (Cell Biology course, Biochemical Cell Metablism course, CAPES). Two members of the unit are co-head in the BioMed Master the course on Cell fate and plasticity. In addition a team leader at CRBM organizes each year a week-long module at the ENS, Paris, on "Multidisciplinary approaches to plant and animal morphogenesis". He is also involved in the EMBO Course on Marine animal models and gives lectures in a global exchange EMBO lecture in Taiwan.

Assessment of the strategy and the five-year plan

The committee supports the novel scientific policy of the CRBM for a unit comprising 18 independent teams, including 7 new teams. The choice of two team leaders to merge their activities in an unique team is logical as well as the decision another team leader and his team to move to another site to develop its research in neuroscience. It is also coherent in view of the heavy workload required for the management of the CRBM that a second deputy director is nominated to take in charge the CRBM infrastructure and technical questions.

In the perspective of the 5-year contract, the CRBM direction plans to carry on the lines of investigation that constitute the historical expertise of the Institute, namely cell cycle progression, cell adhesion, migration, morphogenesis, cytoskeleton organization and post-translational modifications. Furthermore, the Institute is well positioned to integrate quantitative methods in the future research of the teams. Quantitative cell biology aims at understanding how cell molecules are organized in networks and at providing quantitative and large-scale information on their spatio-temporal regulation. These analyses require mathematical modeling and computation. Since the CRBM has developed platforms (MRI and MGC facilities) and has also a close collaboration with the IBC, it is a sound strategy to take advantage of these local infrastructures to develop novel approaches. Another aspect that will be reinforced is the translational research in order to identify novel biomarkers in cancer and to develop molecules that may become drugs to treat bone resorption, bone metastasis and cardiopathies. Finally, it is expected that the constitution of the

Pôle Chimie Balard will facilitate collaborations between biologists and chemists. These general orientations are logical and take advantage of the strengths of the CRBM expertise, of its facilities and of its location on the CNRS campus. Considering the evolution of the CRBM research, it is also desirable that the direction gradually positions the CRBM as an Institute for quantitative cell biology, as suggested, since the name of the Institute does not adequately reflect its actual research. However, addressing the question of quantitative cell biology is an overarching goal and it is not very clear at this stage what the plan of action will be and how concretely the direction will implement this strategy. Concerning, the translational research, there is certainly a real potential at the CRBM but it is by no means specific to this Institute in Montpellier. Thus, the question of the prioritization of research lines that may strengthen the national and international visibility of this Institute persists. However, the CRBM direction members have proved a strong will in the unit restructuring and, therefore, the committee trusts their ability to face this challenge.

4 • Team-by-team analysis

Team 1: Mechanisms of mitosis

Name of team leader: Ms Ariane ABRIEU and Ms Nathalie MORIN

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	4	4
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	2
N6: Other contractual staff (without research duties)	1	1
TOTAL N1 to N6	9	8

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students		
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	5	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	4	4

• Detailed assessments

Assessment of scientific quality and outputs

The team was created in 2011 from the merging of two teams. The team is interested in the control of mitosis in particular in the mechanisms required for accurate chromosome segregation. The team made important discoveries concerning the phosphorylation of key proteins (Cenp-E, Mps1, Ran) essential for proper mitosis progression. For this,

the team used state of the art methods to identify key phosphorylated residues (mass spectrometry, *in vitro* reconstitution of motor motility, live cell imaging…). The demonstration that Cenp-E is a genuine microtubule plus-end directed motor as well as the identification that its tails blocks its motor domain by an *in vitro* motility assay was clearly a breakthrough in the field (Mol Cell 2008). It benefited from a CNRS special press coverage, like two other studies from the team (Curr Biol 2012 and Chem Biol 2011). The discovery that the U62784 inhibitor, first described as a Cenp-E inhibitor, is in fact a cytotoxic inhibitor for microtubules (Chem Biol 2011), was highlighted by numerous newspapers.

These discoveries materialized into 5 publications in high profile (Mol Cell 2008; J Cell Biol 2010; Curr Biol 2012) as well as very good (Chem Biol 2011; Oncogene 2013) journals with the two team leaders as corresponding authors.

Assessment of theteam's academic reputation and appeal

One of the two heads of the team has an excellent international visibility, being invited to 12 international meetings since 2008 and also being part of the organizing committee of conferences (vice-president of the 2010 as well as main organizer of the 2012 Jacques Monod Cell Cycle conference). The other head is a member of the steering committee of the "Cancéropôle Grand Ouest". Both team leaders are reviewers for journals such as J Cell Biol or EMBO J, and participate in thesis committees in France. The team is clearly very attractive since five post-docs (one foreigner) were recruited since 2008 and an invited scientist from IFREMER has joined the team since 2011.

Assessment of the team's involvement in training through research

A single PhD student joined the team from 2006 to 2010. The PhD turned out nicely since it ended up with one publication as first author in Current Biology and one as co-author in Molecular Cell. The extremely low number of PhD students could reflect a poor investment in teaching by the two team leaders as well as by the two CRNS researchers of the team. One permanent researcher has not published since 2008. Maybe the two heads of the team as well as permanent researchers could participate in teaching at the Master level both in international and national courses (one head of the team teaches one course on Mitosis at the Master 2 level).

Assessment of the strategy and the five-year plan

The project is divided into two main avenues. The first part concerns the precise dissection of spindle microtubule dynamics by an *in vitro* approach. This part is very challenging, competitive and ambitious: it proposes to reconstitute a microtubule spindle network using a biomimetic approach. The spindle will be described in the form of its sub-arrays of microtubules (astral, mid-zone, kinetochores) using micro-patterning. The project aims at identifying the minimal set of molecules necessary to organize a functional spindle. This part is funded by an ANR grant (headed by the team leaders) in collaboration with recognized experts in the field. The second part of the project aims at identifying mitotic kinases as well as kinesins up-regulated in a sarcoma cell line and analyze how their deregulation can affect its invasiveness and metastatic potential. This second part is less convincing and the link between the two aspects of the project is rather weak. Furthermore one aims at simplifying things while the other one is addressing an extremely complex process (how representative can ONE cancer cell line be?). Nevertheless, the project is well funded until 2015 by several grants (ANR, FRM).

Conclusion

- **Strengths and opportunities:**

The team originates from the joining of two teams, following an AERES committee. Very encouraging is the fact that the fusion seems to have worked quite well since 2011, with two papers co-signed by the two heads (Curr Biol 2012 and Oncogene 2013).

- **Weaknesses and threats:**

The committee would recommend to focus most efforts on the biomimetic approach of mitotic spindle reconstruction, which is excellent.

- **Recommendations:**

The committee suggests an increased effort to attract PhD students, may be via more involvement in teaching, if it is possible on site.

Team 2: RhoGTPases in osteoclast biology

Name of team leader: Ms Anne BLANGY

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	3
N6: Other contractual staff (without research duties)	2	2
TOTAL N1 to N6	8	8

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	2	

- Detailed assessments

Assessment of scientific quality and outputs

This team provides an outstanding example of "bench to bed side" research, with basic research leading to the characterization of a new molecular strategy for preventing bone resorption up to the isolation of C21 curative compound that they have patented. This team has established the importance of the signaling axis downstream of Vav3 and Dock5 (GEF of Rac1 expressed quite specifically in osteoclasts) in the formation of podosome belt of osteoclasts and the impact of Dock5 over-activation in osteoclasts-driven osteoporosis, with 8 articles published in

very good journals of the field (notably 1 JMBR (IF: 7), J Bone Miner Res (IF: 6.1, 14/122 in endocrinology & Metabolism), 1 Chem & biol (IF: 6), 1 Int J Biochem Cell Biol (IF: 5) and 3 rev articles or book chapters). They have capitalized on a previously established yeast two-hybrid original screening method that they have patented in 2008 and strong knowhow on Rho GTPases (1 PNAS in collaboration with another team to isolate inhibitors of the activation of Rac1 by Dock5. Their unpublished data in mice bring the proof of concept that inhibition of Dock5 activity using C21 compound (patented in 2011) has a great potential for treating bone loss in three different mice models (ovariectomie, rheumatoide arthritis and cancer cell metastasis in bone tissues). Moreover, they have obtained clear data showing that C21 also triggers increase of bone mass (which is not the case for known therapeutic molecules bisphosphonate and Denosumab). Together they have secured more than 1 million euro during the past contract period and have obtained an additional grant from the SATT for the development of anti-osteoporotic compounds directed toward the Dock5-Rac1 axis.

In conclusion, the work of this team provides a very beautiful example of cell biology/biochemistry study leading to translational applications.

Assessment of the unit's academic reputation and appeal

During the past contract, the team obtained several competitive grants (ANR 2012-15, INCa 2011-14, FRM 2009-11, CNRS Valorisation, Arthritis Foundation Courtin, SATT). In total they have secured a total of 1 million euros attesting the quality of the work and the importance of their outstanding findings.

The team was created 9 years ago (2005) and now comprises 1 DR (who is the principal investigator), 1 technician and a full-time associate professor IUT UM2, together with 1 PhD student (Ligue contre le cancer, 1rst year), 2 Postdoc INCa and 2 IR ANR + SATT and two engineer on contract (ANR + SATT). During the past contract a postdoc in the team, has obtained a CNRS CR permanent position and a PhD student has completed her thesis with two articles (1 Int J Bioch Cell Biol and 1 Eur J Cell Biol).

The international and national visibilities of the team leader is excellent, with 1 international meeting organized in Montpellier and 5 invitations in international meetings, notably the J Monod conference.

Assessment of the team's interaction with the social, economic and cultural environment

The team has outstanding interactions with the social and economic environment. They have filed two patents (2008 and 2011) and obtained a grant from the SATT to bring the proof of concept that C21 compound inhibits bone loss, start toxicity assessments, as well as isolate second generation of inhibitors.

The team leader has organized an international meeting in Montpellier. She is a member of the Co-CNRS section 22 and national council of SFBC.

Assessment of the team's involvement in training through research

The team has an excellent investment in mentoring students. One postdoc has obtained a CNRS permanent position in Strasbourg. One PhD student left for a Postdoc in the USA. Taken together, during the present and past contract period 3 PhD students and 4 post-doctoral researchers have or will undergo training in the team.

Assessment of the strategy and the five-year plan

The proposal is directed towards therapeutic applications, based on the proof of concept brought by isolation and study of C21 on osteolytic diseases. Financial support of the SATT has been obtained to achieve this goal. Among all the inhibitors isolated in different screens they will identify first those, which are the more suitable for therapeutic developments (Collaboration with a team at the Institut des Technologies avancées en Sciences du Vivant (ITAV) (Toulouse) and to develop lead compounds (osteoprotective effects versus toxicity) in collaboration with a French company (not yet identified). In addition, the team has started a collaboration with physicists to precisely determine at the molecular level the mode of inhibition of Dock5 by C21. They indicate that they have narrowed down the domain of action of C21 (outside the GEF domain) that most likely acts by allosteric mechanism on GEF activity. Clearly the goal here is, through subcontract to biotechnology companies, the delivery of a therapeutic molecule.

The second aspect deals with more basic research in direct connection with the regulation of the podosome-like belt organization of osteoclasts for cell adhesion and lysis of bone material. The team has identified by proteomic analysis several Dock5 interacting proteins and already pinpointed two important activators (other than ELMO) of Dock5/Rac1 signaling axis. This will be studied by biochemical and cell biology approaches, notably cutting edge PALM microscopy technics.

Conclusion

In conclusion, this team has identified a molecular signaling axis specifically implicated in bone lysis by osteoclasts. They further identified by an original screening method (patented) a first inhibitor of Dock5/Rac1 and brought the proof of concept that inhibition of this signaling pathway can block bone resorption without having inhibitory impact on bone synthesis by osteoblasts. Thus, this original and outstanding basic and translational research is of high potential.

- **Strengths:**

The team has an outstanding high background in a field that represents a major challenge in terms of public health. The team possesses all the expertise and enthusiasm to reach its scientific goals. The proposal is an appropriate balance between basic and translational research which will largely been subcontracted to biotechnology companies. They have identified an activator of Dock5/Rac1 other than ELMO, which represents a regulator of high potential in terms of basic research.

- **Weaknesses:**

There are no real weaknesses for this team. Nevertheless, considering its size we strongly encourage the team leader to pay great attention in prioritizing ongoing projects with the importance of defining precisely at the molecular level the mode of action of C21 on Dock5, in order to secure an outstanding impact publication reporting C21 therapeutic effects.

- **Recommendations:**

The research of the team is remarkable. Given the limited size of the team, the committee strongly recommends that the team leader gives high priority to the main research axis and defines the mode of action of the inhibitor C21 on Dock5.

Team 3: Controlling mitotic entry and progression

Name of team leader: Ms Anna CASTRO and Mr Thierry LORCA

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	4	4
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)	3	4
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	8	9

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

For the past 2 decades mitotic entry and exit was thought to be regulated exclusively through the activation and inactivation of the mitotic kinase cyclin B/Cdk1. Over the past 5 years a major paradigm shift has revealed that phosphatase activity is in fact inhibited during mitosis. The team led was key to this discovery. The team showed that the phosphatase PP2A-B55 is an important player in the regulation of mitosis entry in vertebrates and revealed that a novel kinase named Greatwall indirectly regulates PP2A activity. A major breakthrough in the field was the identification of Arpp19 as a key substrate of Gwl that directly inhibits PP2A-B55. This highly original work was

published in Science in 2010. In addition to the Science article the team published several other articles in high impact factor journals re-enforcing the team already strong track record.

The expertise of the team is also beneficial for the Institute as attested by the productive internal collaborations: Abrieu (Current Biol. 2012), Piatti (Plos Genetics, 2013)

Assessment of the team's academic reputation and appeal

Several top-level personnel have recently been recruited. One permanent investigator joined the team in 2012 and three top-level postdoctoral researchers during the period 2008-12. Two PhD Students started their thesis work in 2012 and 2013. The team is thus well equilibrated in terms of permanent and non-permanent positions for the future.

The excellence of the team was further recognized by the awarding of the prestigious PhD L'Oreal award in 2011 to a previous PhD student (who was first author of the article published in Science). The international visibility of the team is also attested to by invitations to international meetings (7), as well as the organization of an international meeting (CCD, Montpellier 2013). Another indicator of the team's standing is that the team leaders have been asked to write reviews in the ournals Oncogene, Gene and Cancer, as wall as book chapters, attesting their expertise and leadership in this area.

Finally, the team leaders are members of the grant awarding committees ARC and La Ligue.

Assessment of the team's involvement in training through research

The team has been involved in the ongoing training of Ph.D students and also contributes to the teaching at Montpellier University.

The team has been involved in the ongoing training of four Ph.D students, two of them successfully defended their thesis and are currently post-doctoral fellows.

The two team leaders are involved in M1 and M2 courses at Montpellier University.

Assessment of the strategy and the five-year plan

Among the five projects presented four were considered outstanding. One project displayed ambition to study S-phase in addition to mitosis which they have a long standing history of analyzing. The other three projects were well structured, displayed a clear strategy based on the team's strengths and are highly likely to result in a successful outcome. The team has extensive expertise and experience to guide the strategic direction of the projects depending on how they develop. In addition, the strategy of the team displays a good balance between new avenues of research and a continuation of current themes.

More specifically, the team wishes to determine the spatiotemporal association of Arpp19 with PP2A-B55 (PLA and confocal microscopy) and define the phosphoryaltion pattern of Arpp19 throughout the cell cycle in Xenopus and human cells in culture

- investigate the role of endosulfine (ENSA) and the effect of greatwall phosphorylation on ENSA function;

- test the hypothesis that increased PP2A-inhibitory activity of Arpp19 by Gwl overexpression participates in tumoral progression. This part of the proposal is the weakest one at the present stage in our opinion as it is based on a correlation between OE of Gwl and tumorigenesis. Nevertheless the process of moving towards the problematic of tumorigenesis is pertinent and based on a partnership with the team of Mr Marco MALUMBRES (CNIO, Madrid) for the mouse model and with Mr Fréderic CHIBON (Institut Bergonié, Bordeaux) for human biopsies;

- identification of noval Gwl substrates. This task utilizing the Xenopus system which is the trade mark of the team, and three potential new substrates have been identified. This opens the way to new avenues of research;

- identify phosphatases involved in the dephosphorylation of cyclinB-cdk1 substrates. The existence of such phosphatase has been postulated for a long time. The team proposes to use low-tech (phosphatase inhibitors) and high-tech (SILAC to determine the profile of dephosphorylation at mitosis exit) approaches to identify such phosphatases, and to characterize them ex vivo using a proximity ligation assay.

Conclusion

- **Strengths and opportunities:**

The major strength of the team is its international reputation based on an outstanding publication record over the last two decades. One clear opportunity is that the team could capitalize on this series of several very high impact factor articles culminating in the Science article of 2010 to secure funding at an international level.

- **Weaknesses and threats:**

One apparent weakness would be that the team does not appear to impose itself as much on the scientific scene as one would expect from a team that is so well respected and that continues to publish outstanding work. There are no threats.

- **Recommendations:**

That the team continue to do what they clearly do so well and to seek funding at an international level. On a medium to long term scale it may be useful to examine some of the questions in a more genetically tractable model organism (either through the use of gene editing tools or use of a model organism that has conventional mutants available).

Team 4: Ubiqutin-proteasome system and cell cycle control

Name of team leader: Mr Olivier COUX

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	5	5

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	2
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	2	2

- ## Detailed assessments

Assessment of scientific quality and outputs

The team results from the recent merging (2011) of two previous teams working on the regulation of the Ubiquitin/Proteasome System (UPS) and on the control of cell cycle and DNA replication. The team has explored how post-translational modifications by ubiquitin and ubiquitin-like molecules impact on cell cycle control, cell survival and cell homeostasis.

One issue was to understand how the cell controls the degradation of specific cell cycle regulators. The major findings in this field are:

- the demonstration that a failure to degrade the CDC25 phosphatases during mitosis leads to formation of multipolar spindles due to aberrant dephosphorylation of Kizuna, a protein essential for spindle pole integrity;

- the evidence for a key role of the SCF-Fbw7 ubiquitin ligase in the periodic expression of Cyclin E contributing to the control of replication origins during normal cell cycle;

- the observation of the 20S core proteasome in association with its regulator PA28 in nuclear speckles, a site of intranuclear trafficking of splicing factor;

- the demonstration that in the presence of substrates, the 20S core proteasome can fully assemble in active 26S proteasome.

During the 2008-2013-period, the team published 11 original articles, 7 as senior author, in good impact journals notably, 1 Mol Biol Cell (IF : 4), 1 Cell Cycle (IF : 5), 1 Biol Cell (IF : 3.5), 1 Nat Commun. (IF : 10). The team leader was also involved in the coordination of one book focused on the proteasome and the ubiquitin-like proteins; several lab members contributed to chapters.

Assessment of the team's academic reputation and appeal

During the past contract, the team obtained several competitive grants: PI of 1 grant 08/F19 Biophysics (France/Israel); of 1 ANR (2011-2012), 1 ARC (2012-2014), 1 Ligue régionale (2012) and partner of 1 ANR (2009-2010) and FP7 Marie Curie Initial Training network (2012-2014).

The team comprises 4 staff scientists (2 DR2, 1 CR1 and 1 assistant professor (that was recruited in 2010 at Montpellier 2 University) and 1 PhD student).

During the past contract, 4 PhD students completed their thesis, 2 of them with publications.

Two team members have been co-organizers of international meetings or training courses (Atelier INSERM on Ubiquitin; FEBS special meeting on Protein quality control and Ubiquitin; 3rd Cell Cycle and Cancer Meeting, Montpellier).

The team participates in several national and international networks (« Inproteolys » European network, FP7 Marie Curie initial training network, UPStream network, CNRS-GDR 2915 “Replication of eukaryotic chromosomes and its checkpoints).

The team leader is the French coordinator of the European network COST Proteostasis.

The visibility of the team leader is good with 2 invitations to national meetings (Ubiquitin workshop, CEA, 2008; Interactomics workshop, 2012).

The team leader is Associate Editor for BMC Biochemistry and Editor for Biomolecules.

Assessment of the team's interaction with the social, economic and cultural environment

The team had industrial partnerships in the form of contracts for the production of recombinant 26S proteasome and proteasome activity assays.

Assessment of the team's involvement in training through research

Two team members have been in charge of training of 4 students who obtained their PhD (2005-2012).

One PhD student is currently in the laboratory. The assistant professor (MCF) is teaching at the Montpellier 2 University. No information on L3, M1 and M2 students lab training. Online development of a comprehensive course on ubiquitin-dependent degradation (http://www.snv.jussieu.fr/vie/dossiers/ubiquitine/ub0.html).

Assessment of the strategy and the five-year plan

The project for the five next years will be structured around the regulations controlling the expression and the activity of PA28 in cell proliferation, but also in cell resistance to genotoxic stress:

- in order to determine whether PA28 plays a role in the resistance of AML to genotoxic treatment, the team will evaluate its expression and analyze the effect of its downregulation on the chemoresistance of AML cells. (a search for a protease involved in PA28 degradation will be undertaken);

- the biological role of PIP30 in the control of PA28 functions will be evaluated in response to genotoxic stress. The effect of altering PIP30 levels will be investigated in various cellular events controlled by PA28. The team also aims at defining the domain of interaction between PIP30 and PA28 by a combination of structural and mutagenesis studies;

- the potential co-localization of the 20S proteasome / PA28 complex with the heterochromatin markers HP1/ will be further investigated. As HP1 is recruited to various types of DNA damage and are important for DNA repair, this hypothesis is worth investigating;

- using quantitative SILAC proteomic analysis, the team aims at identifying the post-translational modifications and interacting partners of PA28 in the stress response.

The proposal addresses important questions regarding the impact of ubiquitin and ubiquitin-like molecules on cell cycle control, cell survival and cell homeostasis. The project fits with the main axes of the research defined for the CRBM.

Conclusion

- **Strengths and opportunities:**

The proposal will address appropriate questions about the role of PA28 and genotoxic stress response in the context of resistance of cancer cells to chemotherapy. The team has a high background and all the expertise in the field to reach its scientific goals.

- **Weaknesses and threats:**

With 4 staff scientists and only one PhD student the team is unbalanced.

- **Recommendations:**

The committee strongly encourages the team leader to pay attention to prioritizing the ongoing projects and to recruit PhD students and post-docs.

The team should also be encouraged to apply to grants through local and national calls. In particular, effort should be done to secure funding after 2014.

The involvement in International or European programs should also be considered.

Team 5: Signalling and cytoskeletal dynamics

Name of team leader: Ms Anne DEBANT

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	3	3

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	2
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

The team is interested in the mechanisms of action of Rho GTP-binding proteins and upstream Rho-GEF activators, with an emphasis on TRIO and its Rho GTPase substrates. During the past decade, they developed four lines of original research.

First, they discovered that TRIO is required for RAC1 activation in rat cortical neurons in response to binding of the axon-guidance cue Netrin-1 to DCC receptor in a signaling cascade involving TRIO phosphorylation by Fyn (Mol Cell

Biol 2008 and 2013). This pathway contributes to Netrin-1/DCC-induced axon outgrowth. Using MS approaches, they found that Trio interacts with microtubule +tips (EB1, Navs) and is recruited at the + ends of microtubules to define a local control of Rac1 (paper in revision). They also observed that TRIO exerts a role in the anaphase to telophase transition possibly via the recruitment of regulators of cleavage furrow (unpublished), leading to emergence of new investigation proposal.

Second, the team developed promising inhibitors of RhoGEF using peptide aptamer in yeast as an approach (SciBX 2009 and Chem Biol 2009).

Third, using transcriptomic approach with cerebellar Purkinje cells they began to identify Rho GTPase signaling components, and identify DOCK10 (cdc42-RhoGEF) and GTPase TC10. DOCK10 is shown to be required in spinogenesis via Cdc42 (submitted). TC10 is also required for spinogenesis and could act via SHANK/PIX (in preparation).

A fourth project was aimed at characterizing the role of doublecortin (zyg8) (involved in human brain cortex development) in a genetically tractable model organism, *C. elegans*. The study revealed that zyg8 is a microtubule organizer in neurons (J. Cell Sci 2012).

The track record of the team is good: 15 articles have been published, 5 of them as senior author: 2 Mol. Cell Biol. (2008 and 2013), 1 Chem. Biol. (2009), 1 Methods Mol Biol. (2012), 1 J.Cell Sci (2012) and a book chapter.

Assessment of the team's academic reputation and appeal

The team comprises 3 staff scientists (1 DR2/PI and 2 CR1) and 2 Ph.D students. A top level permanent researcher has been recruited in 2009 (CR1 CNRS). The ratio of permanent/non-permanent staff is unbalanced and size is suboptimal. The team should improve attractiveness by recruiting post-docs.

The international visibility of the team is attested by invitations of the team leader to international conferences (CSHL 2008, Jacques Monod 2009 (PI co-organizer), Madrid 2011) as well as the other members of the team (Petites G 2008, 2011, FASEB 2013, Petites G 2008, 2011, Barcelona BioMed 2012). Another indicator attesting the expertise of the team leader is that she is an Editorial member of Biology of the Cell (2010-11) and Small GTPases (2010-11), she organized an international Jacques Monod Conference on small GTPases in 2009, and has been asked to write a book chapter.

Finally, the team leader was a member of the following grant awarding committee: ANR blanc committee (2009-11), ARC committee 4 (2006-2011), canceropole Ile de France (2012-).

Assessment of the team's interaction with the social, economic and cultural environment

Fund raising is good (ANR PCV 2006-08, ANR Blanc Neuro 2008-11, Cancéropôle GSO 2011, Fondation de France 2012-2013), however funding does not seem to be secured after 2013.

3 patents were deposited (2003, 2009) (peptides inhibitors of Trio, antibody to Trio) attesting the originality of the products transferred

Assessment of the team's involvement in training through research

The team appears to be an attractive place for Master and PhD students: 9 M1 or M2 students since 2008 and 3 PhDs.

Assessment of the strategy and the five-year plan

Past achievements raised a number of novel and interesting results (link with MTs +end) opening new lines of research that the team proposes to investigate. Among the three projects presented, two were considered excellent.

The team proposes to investigate the role of Trio in cell cycle control. This is based on the findings by the team that depletion of Trio in HeLa cells causes defect in proliferation, associated with reduced RhoA and pMLC recruitment at the furrow and extensive blebbing. To investigate the potential involvement of Trio in tumorigeneis (in sarcoma development, collaboration with a team in Bordeaux), the team will combine cell biology, biochemistry and *in vivo* tumor xenograft approaches. This part of the project, although original and displaying the ambition to study the role of Trio in mitosis in addition to its role in neurogenesis, is judged risky on the basis on the data available to the committee.

The two other projects are well structured and have a clear strategy based on the strengths of the team acquired over the past fifteen years. They are expected to provide a successful outcome.

The first one is based on available data from the team showing that GKS3beta can phosphorylate TRIO. The impact of phosphorylation on TRIO's interactions with +tips including NAV1 and CLASP2 and consequences for TRIO's association with microtubule +tips will be investigated. Upstream signaling leading to TRIO phosphorylation will be explored in the context of Netrin-1/DCC activation of RAC1. This part of the proposal is doable as all the methodologies are mastered by the members of the team, the basis of the project are robust. Several novel findings leading to important publications are expected.

Second, the team identified a novel function for DOCK10 in neural development that they propose to characterize by proteomic approach on brain to identify new partners of Dock10, and by performing conditional KO in Purkinje cells (KO and Cre lines available) to search for a function of DOCK10 in dendritic spines morphogenesis and migration of granule cells. They also propose to test whether these putative effects of Dock10 are via Rac1. This part of the proposal is solid, novel and very promising.

Conclusion

It is remarkable that despite its strong involvement in the direction of the unit, the team leader was able to maintain such a top-level research.

- **Strengths and opportunities:**

The strength of the team is its international reputation based on original research and good track record over the last fifteen years. One clear opportunity is linked to the hiring of top-level CR1 researcher(s) that should be encouraged to apply to grants through local and national calls

- **Weaknesses and threats:**

One possible weakness linked to the suboptimal size of the team is the development of three distinct projects.

There are no threats.

- **Recommendations:**

To seek funding and attract top-level post-doctoral researchers. If the size of the team were to stay constant, putting everyone's effort on the most promising and advanced project may help publishing in high impact journals and secure funding on the medium to long scale.

Team 6: Cilia Centrsome and Pathologies

Name of team leader: Ms Bénédicte DELAVAL

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	2	2

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		

• Detailed assessments

Assessment of the strategy and the five-year plan

The team leader (CR1 CNRS) has created her team in 2012 at the CRBM. Since the creation of the team, two post-docs were hired and a CNRS technician was appointed to the team. The research of this team is focused on the study of the biological roles of cilia proteins during mitosis and on the pathological consequences linked to their dysfunction. This is an original program exploring the pleiotropic functions of cilia proteins that defines a line of investigation outside of the main scope of the ciliogenesis domain. The project aims at : 1) describing the role of cilia proteins in dividing cells at the molecular and cellular levels; 2) investigating in Zebrafish the *in vivo* relevance of the role of IFT proteins in mitosis and their involvement, when inactivated, in ciliopathies; 3) exploring the role of IFT proteins in stem cell renewal and cancer.

The research program is well defined, original and rests on solidly established results. The team leader is dynamic and her work is already recognized by the scientific community working on cilia. With grants secured until 2016 and a team already comprising two post-docs and an ITA, the perspectives to successfully reach the scientific goals are very good. The general feasibility of the 5-year plan is excellent.

Team 7: Chemical biology and nanotechnology for therapeutics

Name of team leader: Mr Gilles DIVITA

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	5	5
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	6	6

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	X	
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		

• Detailed assessments

Conclusion

During the on-site visit of the AERES committee, a CNRS scientist who joined the team in 2012 presented the past activity of the team and the strategy for the five-year contract. Although the committee members acknowledge the praiseworthy effort of this scientist, they considered that they were not in a situation to proceed to a complete and fair evaluation in the absence of the team leader. In these conditions, the committee decided not to proceed to the assessment of both the scientific activity and the team future program. However, the committee members unanimously estimated that the research of this team focused on the conception of nanotechnology devices used to deliver therapeutic biomolecules does not integrate properly in the scientific mainstreams defined by the CRBM direction for the five-year contract. Therefore, the committee strongly recommends that the scientists working in this team seek an integration in other academic laboratories working on similar or more complementary topics in order to strengthen the synergy with their own research.

Team 8: Adhesion, RhoGTPases and physiopathology of skeletal muscle

Name of team leader: Ms Cécile GAUTHIER-ROUVIÈRE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	3
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	6	6

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	

• Detailed assessments

Assessment of scientific quality and outputs

This team addressed challenging questions in cell biology related to the function of cadherin adhesion molecules in the dynamic of cell-cell junctions (CCJ). This proposal involves cutting edge 3D-structured illumination microscopy technics and proteomic approaches. In addition, they investigate the molecular mechanisms linking cadherin dysfunctions and rhabdomyosarcoma tumor progression.

One main and original achievement of the team in the field was to highlight the role of cholesterol-enriched microdomains (DRM) and Flottilin in stabilizing CCJ. They have also identified Flotillin molecule as a new partner of

Cadherin. Their findings are published in good and recognized journals of cell biology and biochemistry : J Biol Chem (2009) and J Cell Sci (2013).

An original axis of their research deals with the study of the function of Cadherin-based cell-cell adhesion in myoblast fusion. The team identified two key drivers of myoblast fusion: i) the atypical small GTPase RhoE, a negative regulator of RhoA/ROCK pathway and actomyosin contraction, and ii) ARF6, an activator of phospholipase-D enzyme that triggers a flux of phosphatidic acid at membranes (published in Cell Death Diff 2008, MBoC 2010 and 2013). A third axis of their studies deals with the study of the dysregulation of cadherin-based cell-cell adhesions in rhabdomyosarcoma, a skeletal muscle derived sarcoma. Alveolar ARMS are very aggressive tumours driven by the fusion of either Pax3 or Pax7 genes with Foxo1A. Pax3-FOXO1 ARMS tumours have an extremely poor prognosis, as compared to Pax7-FOXO1. Through a collaboration with the CIT program of Ligue Nationale Contre le Cancer and in collaboration with Mr Olivier DELATTRE (Institut Curie, Paris), the team identified P-cadh and ArhGAP25 (a GAP for Rac1), as genes selectively up-regulated by Pax3-FOXO1 (the work was published in Cancer Res. 2008 and Oncogene 2013).

The track record of the team is very good to excellent, with the team leader publishing a high number of original papers as last author (11), in well recognized journals of cell biology, biochemistry and cancer research (JBC, JCS, MBC and Cancer Res or CDD).

Assessment of the team's academic reputation and appeal

During the past contract, the team obtained several competitive grants (ANR 2007-09, INCa 2009-11, Equipe Labellisée Ligue 2008-11/2012-14 and AFM). This attests the importance of the questions addressed and the quality of the past achievements. This team has secured grant up to the end of 2015.

The team was created 15 years ago (1998) and now comprises 1 DR (who is the principal investigator), 1 MCU, 1 IR and 3 PhD students (1, 3 and 4 years of thesis). 3 postdocs (fellows ARC and INCa) and 2 PhD students joined the lab during the evaluation period and left. One post-doc has obtained a CR1 permanent position further attesting the quality of mentoring provided by the PI.

The international and national visibility of the team leader is excellent, with 12 invitations in international conferences (Gordon, Jacques Monod ...) and 3 meetings organization (2 x Imaging the Cell & When Dev meets Cell Biol).

Assessment of the team's interaction with the social, economic and cultural environment

The team has excellent interactions with the social and cultural environment. The PI is highly involved in the organization and dissemination of the field of cell biology in France, as a member and then President of the French Society of Cell Biology (2010-12). The team leader organized several international conferences with conferences aimed at promoting the field of cell biology to a broad audience (Imaging the Cell 2008 and 2010, When development meets cell biology 2012).

Assessment of the team's involvement in training through research

The team has an excellent investment in the training of students at all levels (Master, PhD and postdoc). This team has attracted 4 Master students with two of them having obtained their PhD (2008, 2011) with one first author paper each (Cell Death Diff 2008, JCS 2013). 3 PhD students are currently in the lab, one in co-supervision with a laboratory abroad (Ms Claudia MERMELSTEIN's team, Univ. Rio de Janeiro, Brazil). One postdoc has obtained a permanent position at the CNRS.

A MCU member in the team has teaching duties (L2/L3 and M2 levels at UM2) and is a member of CNU sections 64 and 65 at Montpellier-2 University. In addition, the team leader is giving a lecture for Master-2 students each year at Montpellier University.

Assessment of the strategy and the five-year plan

The two major tasks of the future projects of the team are in direct continuity with past achievements. They are aimed at deciphering the role of Flottilins in cadherin-dependent regulation of CCJ (AIM1) and decipher the role of P-cadherin (AIM2-axis1: P-cadherin and collective cell migration) and ArhGAP25 (AIM2-axis2: ArhGAP25 and cell invasion) in rhabdomyosarcoma cell invasion.

AIM1: The role of flotillins will be analyzed by a KO approach in vivo during gastrulation in zebrafish, which requires a fine balance of E- and N-cadh based cell-cell adhesion. In parallel the impact of the up-regulation of flotillin in skeletal muscle tumors will be investigated at the level of cell-cell and cell-substrate adhesion as well as during cell invasion.

AIM2: The role of P-cadherin on matrix remodeling during tumor cell invasion through biglycan and decorin expression will be determined. Based on the strong expression of ArhGAP25 in most aggressive alveolar subtype tumors the role of this Rho-GAP will be analyzed during tumor cell invasion in 3D reconstituted environments and during experimental metastasis in zebrafish xenograft model. The project is based on a good combination of *in vitro* and *in vivo* approaches with the development of xenograft models in zebrafish. It will be of importance to keep a focus on rhabdomyosarcoma model system to fully reveal the relevance of P-cadherin and ArhGAP25 dysfunctions in cancer progression.

Conclusion

The understanding of the spatio temporal control of CCJ by cadherin adhesion molecules although it is a challenging question is an outstanding question to be solved. It is of major importance notably given the clear implication of cadherin-based dysregulations in the capacity of tumour cell invasion. This excellent project is based on preliminary data. This research program is entirely feasible, with different research teams at CRBM aiming at developing zebrafish as a model system. The proposal represents a good balance between secured and risky tasks.

- **Strengths:**

The team has a very good to high background in a highly competitive domain of cell biology. Team members possess all the expertise and are located in a very good environment to reach their scientific goals. The proposal is an appropriate balance between doable and more novel/risky projects (rhabdomyosarcoma model system). They have pinpointed a role of DRM and flottilin in the control of CCJ that is original in this field and should brought important insights in our understanding cell-cell junction plasticity.

The team is located in an institute and campus, which are developing cutting edge microscopy technics (MRI Imaging Facility, RIO/IBiSA) and have as a priority to implement Zebrafish animal facility in the institute (with the expertise of Ms B Delaval, ANR Chair of Excellence).

- **Weaknesses:**

The team good international visibility would be promoted by publishing in generalist journals of high rank, rather than by following a policy of high number of publications in journals of specialty.

This would become easier by balancing the ratio between PhD students and postdocs and establishing a collaboration with teams having an excellent background in the fields of rhabdomyosarcoma and collective cell migration.

- **Recommendations:**

Keep the focus on the main research lines explored by the team that have proved innovative and productive. Try to strengthen the international reputation of the team by publishing in jounals of higher impact.

Team 9: Gene expression regulation

Name of team leader: Mr Dominique HELMLINGER

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	3	3

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended		
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		

• Detailed assessments

Assessment of the strategy and the five-year plan

The team leader joined the CRBM in 2011 to establish a junior team financed by the ATIPE-Avenir program. Funding was extended to two successive FRM post-doctoral fellowhips, a 2013 Canceropole Emergences grant. The team leader received the CNRS prime d'excellence in 2012.

The team performs important work on the mTOR kinase signaling pathway and the SAGA transcriptional co-activator complex implicated in processes that allow cells to respond to changes in nutrient levels. Team members will also study the function of the SAGA subunit Tra1 in the ASTRA complex, which is also linked to TOR regulation. Overall, this is an ambitious and original program. However, the team leader should pay attention to not diversify its main research too much and try to establish too many different model systems for his project.

Team 10: Structural bioinformatics and molecular modelling

Name of team leader: Mr Andrey KAJAVA

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	3	3

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	5	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	2	2

- ## Detailed assessments

Assessment of scientific quality and outputs

The Kajava team employs methods of bioinformatics and theoretical structural biology to understand principles of protein structure and interaction of macromolecules. Their goal is to develop bioinformatics tools to analyze sequence-structure and function relationships on large scale.

Their major achievement is the development of the T-REKS program that identifies new tandem repeats in proteomes. They also set up a database for tandem repeat containing proteins and developed tools to classify their 3-D structures. Notably the software is freely available to the scientific community. Employing these tools, they discovered what they call a pathogenic fold present in disease-related polymers. They further applied their bioinformatics tools to identify malaria vaccine candidates that have been tested experimentally. Together, the team has a good mix of developing important new bioinformatics tools and applying them to biological problems in collaboration with experimentalists.

The overall scientific output of the team is excellent with 30 publications (20 original publications (13 as a first and/or last author) and 10 reviews in good journals (JBC, J. Struct. Biol, Bioinformatics and 1 co-author in PNAS). A number of publications are important collaborations indicating their integration in the scientific community.

Assessment of the team's academic reputation and appeal

The team leader was invited to give oral presentations at 12 international conferences and workshops and 24 seminars in laboratories in France and abroad. The team attracted 3 post-docs and 5 graduate students (2 graduated) and was/is active in interregional collaboration programs with Spain and Russia. The team leader was involved in the organization of a Jacques Monond Conference, he is a member of the editorial board of the Journal of Structural Biology and serves as a reviewer for several important journals. He also participates in the direction of the new "Institut de Biologie Computationnelle", which concentrates all computational biology in Montpellier financed by an ANR Investissement d'Avenir. In conclusion, the head of the lab has a very strong international visibility.

Assessment of the team's interaction with the social, economic and cultural environment

The team's development of bioinformatics tools and databases is an important service to the scientific community.

The team's work was presented in a "communiqué de presse" by the CNRS and they disseminated their work in a publication for the general public (Pour la science).

Assessment of the team's involvement in training through research

Five PhD students were recruited since 2008, two graduated with four and one first author paper, respectively. The team also attracted 3 post-docs in the past. Team members are involved in teaching and the direction of the doctoral school. One course has an "Erasmus mundus" label. The team leader teaches at the M2 level.

Assessment of the strategy and the five-year plan

First the team wants to build on their strength to further develop tools to better identify tandem repeat containing proteins, with the focus on globular domains.

The second focus is on structure prediction and molecular modeling of proteins containing repeats.

Third they will continue to analyze and characterize amyloidogenic regions in proteins.

Fourth they intend to design proteins with novel functions, such as coil fibrils that can be useful for nano-technological applications.

Overall, this is a solid and ambitious research program, parts of which require tight collaborations with experimentalists.

Conclusion

- **Strengths and opportunities:**

The team is highly visible in the identification of protein repeats. Their application of their tools to identify fibril forming proteins is novel and interesting. Their research topics should be attractive for international EU networks.

- **Weaknesses and threats:**

Future funding has to be secured beyond 2013! No post-docs are currently working in the team. The contribution of two senior researchers to the current research program is not evident.

- **Recommendations:**

Concentrate the research and look out for national and international collaborations to test and verify the hypothesis defined by bioinformatics.

Team 11: Transcriptional control of chordate embryogenesis

Name of team leader: Mr Patrick LEMAIRE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	3	3

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	4	2

- Detailed assessments

Assessment of scientific quality and outputs

The team joined the CRBM in 2011. Over the past five years the team has had a major impact on the emerging ascidian model to study fundamental questions in developmental biology such as the mechanism of gastrulation and transcriptional control of embryonic development. The scale of the research was ambitious in its scope. A web-based computational framework (Aniseed) was developed by the team to organize genomic, anatomical, and expression data within a virtual 3D embryo visualization environment that is now available as an open-access platform that is used by the international ascidian community.

To answer their biological questions the research team has taken a highly original path including the development of ChiP-seq methodology, the creation of in toto imaging techniques, and the analysis of the transcriptional control during embryogenesis revealing the cis regulatory logic and also how nucleosome occupancy varies. In addition, the team was the driving force behind the sequencing of four ascidian genomes which are now available for public viewing/analysis on the Aniseed platform. Much of the work has been published in highly rated journals (including four Current Biology articles and one Cell article).

Assessment of the team's academic reputation and appeal

Several high level personnel have recently been recruited. One research director in 2012, one research engineer in 2011, three PhD students (2011-2013) and one software engineer in 2013. The team is thus well-balanced and equipped for the coming years.

The academic impact of the team is well-founded. The team leader was recently elected as an EMBO member in 2011. The team participates in several scientific networks (the Dopaminnet EU project, the Epigenmed Labex, and the Morphoscope Equipex). The team leader has been invited to 19 national/international conferences including a keynote session in Montreal as well as organizing 3 scientific meetings. Another indicator of the team's standing is that the team leader is on the editorial board of Development, Genesis and Developmental Biology.

Finally, the team leader is a member of the ERC LS3 panel for Starting grants (2011-2016), and a member of the scientific advisory boards of the TEFOR infrastructure and CRG-EMBL systems biology unit (Barcelona).

Assessment of the team's interaction with the social, economic and cultural environment

The impact of the team on the social and cultural environment has come through the development of community tools such as Aniseed which is used by the international scientific community. This interactive platform combines genomic, transcriptomic and anatomical data in an easy to use environment. Also following election to become an EMBO fellow the team leader was interviewed on TV (FR3).

Assessment of the team's involvement in training through research

The team leader organizes and participates in national and international teaching: a yearly week-long lecture module at the ENS Paris, Masters teaching (Institut Curie Paris, UPMC, Paris, Montpellier University 2, Lyon ENS). The team leader is also involved in teaching at an international level : EMBO course on marine animal models (Kirstenberg, Sweden) and a global exchange lecture course (Taipei, Taiwan). Other members of the team also participate to teaching either through co-supervision of PhD students or via teaching on Masters courses.

These efforts to transfer knowledge to a wide and varied audience are outstanding.

Assessment of the strategy and the five-year plan

The main goal of the team is to determine how patterns of evolutionary divergence can be uncoupled from morphology. For this the ascidian model has been chosen because they display genomes that have diverged considerably in species that last shared a common ancestor more than 500 million years ago yet at the morphological level these species produce embryos that appear almost identical.

To understand this phenomenon of evolutionary divergence coupled with morphological stasis the team proposes a three pronged approach: 1) Quantification of cell shape and embryo morphology through advanced live in toto imaging. 2) Analysis of transcriptional networks and sequenced genomes to identify the cis and trans regulatory logic that control cell behaviour up to the gastrula stage, and 3) Re-sequencing of 10-20 Ciona individuals to identify signatures of selection and developmental constraint. This multilevel approach ranging from the development of advanced imaging techniques to perform in toto analysis of cell shape during embryogenesis to identify conserved features which will inform the transcriptional, genomic and population genetics approaches is highly original. The team plans to extend their analysis to include population genetics to identify signatures of selection and constraint. The team spearheaded an international effort that resulted in the sequencing of paired ascidian genus genomes, then brought together experts from the international community to assemble and annotate the sequenced genomes. They also then developed the tools to perform ChiPseq, nucleosome occupancy and cis/trans regulatory analyses to uncover the transcriptional regulatory logic conserved within and among ascidian species. Over the past 4-5 years the team has created the methodologies to address their questions and has thus put in place the foundations to ensure the greatest possibility of success of these ambitious goals.

Conclusion

- **Strengths and opportunities:**

The major strength of the team is its international reputation based on an outstanding publication record and development of community-based genome/transcriptome/anatomical browser (Aniseed) over the last 5 years. One clear opportunity is that the team could capitalize on this series of several very high impact factor articles and international reputation to secure funding at an international level.

- **Weaknesses and threats:**

There are no weaknesses or threats identifiable.

- **Recommendations:**

To continue to perform outstanding research.

To seek funding at an international level.

Team 12: Mitotic regulation of chromosome partitioning and cell division

Name of team leader: Ms Simonetta PIATTI

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)	1	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	2	1

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	5	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	

• Detailed assessments

Assessment of scientific quality and outputs

The head of the team joined the CRBM in 2009 as team leader on an external extremely competitive CNRS DR2 position. The team focuses on how mitotic processes are regulated in yeast to preserve genome stability. Contrary to most eukaryotic cells, Phosphatase 2A (PP2A) promotes mitotic entry in budding yeast. In collaboration with one team in the CRBM, they showed that the Greatwall/Endosulfine/PP2A module is conserved in yeast but that it is used differently to promote PP2A activity. The team used yeast genetic to unravel pathways, which influence mitotic

slippage. They discovered that the conserved chromatin remodelling complex RSC is a key regulator of the balance between mitotic exit and mitotic slippage, a major transition in cancer treatment. Eventually they identified important players in the Spindle Positioning Checkpoint present in yeast. These major discoveries were published in high profile (J Cell Biol 2010; Plos Genet 2012, 2013) as well as in a very good journal (Mol Biol Cell 2009) with the team leader as last author. The team also published work in collaboration in two excellent journals (Curr Biol 2012; Dev Cell 2013).

Assessment of the team's academic reputation and appeal

The team leader was invited to 6 international meetings, to 7 seminars and organized two international conferences (15th European Cell Cycle conference and an EMBO workshop). The PI is a referee for granting agencies (ANR, Wellcome Trust, BBSRC) and a reviewer for excellent journals where she publishes, such as for example EMBO J, PLos Genet, J Cell Biol, Curr Biol. The team leader is a member of the French Society for Cell Biology and a coordinator of the Cell Cycle axis of the Labex EpiGenMed.

Assessment of the team's interaction with the social, economic and cultural environment

There is no mention of the team interaction with the social, economic and cultural environment.

Assessment of the team's involvement in training through research

Three PhD students were recruited since 2008. One ended up with two first author papers (Biol Chem 2011; PLos Genet 2012). Three post-docs published as first authors or co-first authors and all of this with the team leader has sole and only permanent researcher.

Assessment of the strategy and the five-year plan

The project is excellent and extremely solid. It will use a variety of approaches to tackle three main objectives: mapping of all yeast Septins' phosphorylation sites, identify how two, previously identified by the lab, E3-ubiquitin ligases (Dma1 and 2) regulate the actin cytoskeleton for the control of cytokinesis, identify by a genetic screen other factors required in the control of mitotic slippage. The aims of the project are very well defined and will no doubt allow the identification of conserved pathways, which regulate these important steps in mitosis and in cancer cell divisions.

Conclusion

- **Strengths and opportunities:**

The research conducted by this team is excellent, founded by prestigious agencies (ARC, ANR, FRM, Telethon, Fondation de France) using very solid yeast genetics to address key aspects of mitosis regulation. The team has a very good international visibility and produced important results during the previous contract. Furthermore it has a huge potential for novel discoveries (especially the part of the project related to the role of the RSC and SAGA complexes in the control of mitotic slippage).

- **Weaknesses and threats:**

The committee strongly encourages the head of the CRBM to support this team with as least the help of a technician. This help would give more time to the PI for mentoring and might favour even better scoring of the students and post-docs.

- **Recommendations:**

It might be important to help the PI to participate in teaching in order to have the opportunity to attract the best students. Based on the impressive presentation the PI gave in front of the AERES committee, the team leader would certainly be an amazing teacher.

Team 13: Tyrosine kinase signalling and oncogenesis

Name of team leader: Mr Serge ROCHE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	4
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	7	7

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	6	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	5	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

This team is internationally recognized for its research on the non-receptor Tyrosine kinase Src and its implication in the promotion of tumour cell invasion. During the past five years, the team has established the importance of the signalling axis downstream of Src. Its major contributions to this field are:

1) the identification of the Src-like adaptator protein (SLAP) which coordinates ubiquitin- and phosphorylation-mediated control of Src signalling; 2) the demonstration that a strong Src oncogenic activity in metastatic colorectal cancer (CRC) relies on downstream protein kinases such as FAK, MET, the ephrin receptor EPHA2 and the kinase

SGK223; 3) the discovery of the pro-tumoral function of the vesicular trafficking protein TOM1L1 which promotes invadopodia formation and cell invasion; 4) the identification of DDR1 as a new TK receptor for collagen that mediates CRC cell invasion.

These discoveries were published in two high profile journals (J Cell Biol 2008 and Nature Commun 2013) as well as very good journals (Oncogene 2008; Cancer Res 2009; Oncogene 2010; Mol Cell Proteomics 2012) and more specialized journals (PLos One 2011) with the team leader as last author. The team also published work in collaboration in two excellent journals (Blood 2011; Leukemia 2013). Thus a total of 11 articles were published during the contract.

Assessment of the team's academic reputation and appeal

During the past contract, the team obtained several competitive grants: Ligue Label (2009-2011), PI of 2 INCA grants (2006-2009 and 2011-2014), of 2 ARC fellowships (2008 and 2012), co-PI of an alliance SERVIER (2012-2015) and partner of the PHUC-CAPTOR (investissement d'avenir (2013-2018), 3 INCA grants (2008-2011 ; 2009-2012 and 2013-2016), 1 ANR (2009-2012). In total the PI has secured funding until 2018 attesting the quality and the importance of the work.

The team was created in 1997 and now comprises 1 DR (who is the principal investigator), 1 CR, 1 CDI CNRS, 1 IE CNRS, 1 MCU UM2, together with 3 post-docs and 2 PhD students. During the past contract, 4 PhD students completed their thesis with several publications (1 Oncogene, 1 Cancer Res., 1 blood, 1 leukemia, 1 Nat Commun) and one post-doc with 1 publication (Mol Cell Biol).

The team leader is a member of the scientific board of *Cancéropôle Grand Sud Ouest* created to foster strong links between scientists and clinicians. The team's involvement in international and national projects is also attested by the participation of the team leader as member or coordinator of several national (University of Montpellier, Canceroplole CGSO, SIRIC) and international (GDRI France-Japan) research programs.

The international and national visibility of the team leader is good with 4 invitations in recognized international meetings (European association of Proteomic, European Association of Endocrinology.)

The team contributed to the organization of several meetings and workshops (Communication Graduate Student Organization) in Toulouse and Montpellier (4 CGSO meetings and 5 CGSO workshops).

The team leader is part of the management board of the CRBM as deputy director in charge of the scientific strategy and technical matters.

Assessment of the team's interaction with the social, economic and cultural environment

The team has contracted industrial partnerships with Servier, Biorealites, Pierre Fabre, and has scientific interactions with Eurisotope and Novartis.

Team members are regularly involved in knowledge dissemination in the media in the form of communications/interviews for charities (ARC, Ligue Contre le Cancer) and local radios or TVs.

Assessment of the team's involvement in training through research

In the previous contract, the team has attracted a good number of PhD and postdoc students (5 PhD and 4 postdoc) and nowadays, is well-balanced between permanent positions and students/post-doc with non-permanent positions.

Team members are involved in Master, L1, 2, 3 and undergraduate training programs at the Montpellier, Paris Diderot and Toulouse universities.

Assessment of the strategy and the five-year plan

The team will focus on three axes based on available data regarding the tumour suppression function of SLAP and the role of TKs that are downstream of Src.

Project 1: In depth proteomic analysis has revealed the existence of several SRC effectors that are destabilized by SLAP in CRC. In particular, SLAP inactivation in CRC leads to EPHA2 and mTOR2 activation. Using cutting-edge phospho-proteomic analysis, a potential functional link between these two kinases will be investigated.

Project 2: The team's challenge is now to characterize the atypical SGK223 kinase at the molecular and cellular levels, through the identification of its substrates and the development of specific pharmacological inhibitors.

Project 3: The team has to his credit the discovery that the pro-hormone Progastrin (PG) which is abundantly secreted in CRC cells contributes to SRC upregulation. How PG impacts on SRC activity is currently unknown because no specific receptor for PG has been identified. The team's hypothesis is that MET could be a receptor, or a co-receptor for PG. Since MET appears as a downstream SRC target, this challenging hypothesis is worth investigating.

In conclusion, this team has identified a signalling axis downstream of Src and demonstrated its importance in the promotion of tumour cell invasion.

This original and excellent basic research is of high potential and fits well with the main axes of the research defined for the CRBM.

Conclusion

- **Strengths and opportunities:**

The team has an outstanding high background in his field and possesses all the expertise to reach its scientific goals. In particular, the easy access to cutting-edge phospho-proteomic analysis will be essential to decipher in-depth the Src signalling network.

- **Weaknesses and threats:**

There are no real weaknesses for this team. Nevertheless, as it is known that cancer cells with high Src activity may be a clinical predictor of metastasis and bone relapse (Zhang, Cell, 2013), the committee strongly suggests to develop collaborative projects with the other teams from the CRBM involved in the study of bone lysis by osteoclasts.

Since the Src signalling network also relies on stabilization/degradation of many Src substrates and increasing evidence has revealed a functional interplay between phosphorylation and ubiquitination, the team may take the opportunity to collaborate with other teams at the CRBM, to investigate the contribution of the Ubiquitin/Proteasome System (UPS) in Src signalling.

- **Recommendations:**

We strongly encourage the team to continue to perform an excellent research. On a medium to long term scale, the team should pay attention in prioritizing the projects to concentrate the efforts on a limited number of tasks to be able to publish in high profile journals.

Team 14: Dynamics of cell invasion in cancer

Name of team leader: Mr Pierre ROUX

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		1
N2: Permanent EPST or EPIC researchers and similar positions	3	4
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	4	6

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	5	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	2

• Detailed assessments

Assessment of scientific quality and outputs

The team examined how p53 isoforms and Rho signaling pathways control epithelial-mesenchyme (EMT) or epithelial amoeboid transition (EAT) in colon and breast cancers.

The scientific production was judged of good quality for a team involving one DR, two CR and one IR (13 publications in the last five years, 4 articles as senior author including: Methods in enzymology (2008), J. Cell Science (2010), PlosOne (2012), Nucleic Acids Research (2012)).

As the team will benefit from the joining of new members due to internal restructuration of CRBM, achievements were separated in two parts which however clearly demonstrate connections if not between people at

least on the science. Important role of p53 mutants or splice variants in EMT transition as well as in transcriptional reprogramming and invasion was demonstrated involving notably RhoA signaling. New therapeutic drugs that target p53 isoforms were generated throughout the creation of a biotechnology company called Splicos. PAI-1: an extracellular factor was found to participate to RhoA activation. Having initially worked on neural crest development, the new member's work establishing for instance a role for RhoV in the early response to WNT/beta-catenin pathways will now focus on the intestinal epithelium and colon cancer.

Assessment of the team's academic reputation and appeal

Several top-level personnel have been recruited over the past five years. One CR1 was recruited in 2009, one MCU in 2009, one post-doc in 2008. For the coming contract, the team is restructured with one DR, one CR and one MCU whose expertise is in the field of Rho-GTPase signaling and alternative splicing respectively will join the team. Two Ph.D students started their thesis work in 2012 and 2013. The team is currently unbalanced in terms of permanent versus non-permanent positions; a recommendation is to hire post-docs.

The awarding of the Prize ARC foundation 'Alexandre Joël' to a previous Ph.D student also recognizes the quality of the team.

Finally, one DR was a member of Co-CNRS committee (section 22), associate Editor of Biology of the Cell and one CR was a member of an INSERM committee (section 2).

The team leader is the co-founder of SPLICOS SAS and reviewer for several high impact journals including Current Biology, EMBO J., Gut and J.C.B.

Involvement in one of the eight French SIRIC (Site of Integrated Research on Cancer, INCA). Involvement in one ANR in the last five years (joining member).

Assessment of the team's interaction with the social, economic and cultural environment

The activity of the team leader in co-funding the CNRS spin-off Splicos SAS is outsanding. Overall 5 international patents with licensing were obtained on the basis of the team's work during the last five years.

Industrial partnership with SPLICOS.

New members joining the team are also involved in two additional patents.

Assessment of the team's involvement in training through research

Five PhD students were recruited within the last five years, 3 of which have already successfully defended their PhD.

The team contributes to training and education throughout Master courses, with one DR responsible for the M2 course 'control of cell fate'.

Assessment of the strategy and the five-year plan

The scientific project of the team is essentially a continuation of the previous work and benefits from the arrival of two researchers expert in the field of Rho GTPAses. The project is aimed at further characterizing the signaling pathway controlled by a spliced variant of p53 and Plasminogen Activator Inhibitor-1 (PAI) secreted by stromal fibroblasts in Rho GTPase-dependent amoeboid cell shape morphology acquisition, leading to cell invasion. The project relies on the use of colorectal cancer cells, a pertinent model system mastered by the team members, and a series of high throughput analyses of intracellular and extracellular programs leading to cell invasion.

The first aim is well structured, present a clear strategy based on the merged teams strengths, is in direct continuity with the team leader past achievements and are likely to be successful. The two other aims which relies on three distinct -omics approaches will undoubtedly lead to the identification of novel biomarkers. However, due to the size of the team, special attention should be given by the team leader to avoid dispersion, and to concentrate the efforts on the characterization of novel molecular mechanisms rather than simply identifiy novel biomarkers. This should ultimately enable publication in high impact journals in order to secure funding on a medium to long term scale.

Conclusion

- **Strengths and opportunities:**

One clear opportunity is the merging of two sub teams that share common scientific interests and complementary expertise. The team leader is now back to fundamental/academic research after four years spent to develop SPLICOS SAS and funding is secured until the end of 2015, thanks to an industrial partnership.

- **Weaknesses and threats:**

As the project involves several high throughput approaches, a special attention should be given to keep focus on specific fundamental questions while handling large data sets.

A potential threat resides in the ability of the team leader to maintain a strict border between fundamental research at CRBM and applied research at Splicos.

- **Recommendations:**

The arrival of the DR and CR CNRS researchers will be fruitful to accomplish these ambitious projects. Raise funds, hire post-docs, and prioritize the projects to focus on a limited number of tasks to be able to publish in high profile journals. This will enable the team leader to secure funding at the international level on a medium to long-term scale. The involvement in International or European programs should be considered.

Team 15: The response of ubiquitin and ubiquitin-like molecules to cellular stress

Name of team leader: Mr Dimitris XIRODIMAS

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	1	1

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of the strategy and the five-year plan

The team leader established his team in 2011 at the CRBM. The team comprises 2 post-docs and two contract engineers. The team leader and his coworkers have been studying the biological functions of protein neddylation by the NEDD8 pathway. The conjugation of this ubiquitin-like molecule is involved in a wide array of processes and the team has demonstrated the involvement of NEDD8 in the nucleolar stress response. The project aims at : 1) characterizing the role of NEDD8 during nucleolar stress (describe changes in the nucleolar proteome when the NEDD8 pathway is inhibited, determine the role of NEDD8 targets in the nucleolar signalling); 2) investigating the function of NEDD8 as a sensor of various stresses (heat shock, oxidative, etc.); 3) using the model organism *C. elegans* to analyse the contribution of NEDD8 in the DNA damage stress-response and in nucleolar signalling.

Overall, this research program is very well thought out, addresses relevant questions that may have an impact in oncology since NEDD8 inhibitors are in clinical trials. The team leader is very active, has a steady scientific production, co-organized two international meetings and has obtained different funding including an ATIP/AVENIR. The general prospect for the 5-year plan is excellent.

5 • Conduct of the visit

Visit dates:

Start: 05.12.2013 at 8 a.m.

End: 06.12.2013 at 6 p.m.

Visit site: CRBM-CNRS

Institution:

Address: 1919 Route de Mende 34293 Montpellier

Programme of visit:

December 5, 2013

8:00 Welcome to the committee

1. Centering of the committee

8:15 Preliminary meeting of the committee (closed hearing)

Attending: Committee members, AERES scientific delegate

2. Scientific part (session 1)

9:15 Presentation of AERES evaluation and of committee members *(J. Baratti and M. Billaud)*

9:30 Presentation of the unit : A. Debant

Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members

10:30 Scientific Presentation: 2 teams T. Lorca/A. Abrieu

Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members

11:30 Break

11:45 Scientific Presentation: 2 teams - S. Piatti/B. Delaval

Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members

12:45 *Lunch - buffet / discussion*

14:15 Scientific Presentation: 3 teams - A. Debant /A. Blangy/C. Gauthier-Rouvière

Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members

15:45 Break

16:00 Scientific Presentation: 3 teams - P. Roux/S. Roche/O. Coux

Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members

17:30 First meeting of the committee (closed hearing)

Attending: Committee members, AERES scientific delegate

19:00 End of first day

December 6, 2013

2. Scientific part (session 2)

8:15 Welcome to the committee

8:30 Scientific Presentation: 3 teams - D. Xirodimas/A. Kajava/D Helmlinger

Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members

10:00 Scientific Presentation: 2 teams - P. Lemaire/P. Boisguerin

Attending: Committee members, AERES scientific delegate, representatives of Institutions and unit members

11:00 Break

3. Meeting with representatives of Institutions

11:15 *Attending: Committee members, AERES scientific delegate, representative of institution: MERCIER Jacques (University of Montpellier 1), GODELLE Bernard (University of Montpellier 2), FERVEUR Jean François (CNRS-INSB)*

4. Meeting with researchers, technicians, doctoral students and post doctoral fellows

11:45 *in parallel the committee splits into three groups.*

Meeting with researchers

Meeting with technicians

Meeting doctoral students and post doctoral fellows

Attending: Committee members, AERES scientific delegate, without the leaders, representative of institution, without the direction of the unit and without team leader

12:15 *Lunch - buffet / discussion (60 min)*

5. Meeting with the Director of Doctoral School

13:15 *Attending : Committee members, AERES scientific delegate, and ED Director: DESARMENIEN Michel*

6. Meeting with the unit Director

13:30 *Attending : Committee members, AERES scientific delegate*

7. Debriefing of the committee

14:00 Deliberation of the committee (closed hearing)

Attending : Committee members, AERES scientific delegate

18:00 *Thanks and leave of the committee*

18:15 *End*

6 • Supervising bodies' general comments

nouvelle université de Montpellier
un projet, une ambition

UNIVERSITÉ MONTPELLIER 2
SCIENCES ET TECHNIQUES

Le Président

Montpellier, le 28 avril 2014

M. Didier HOUSSIN
Président de l'AERES

M. Pierre GLAUDES
Directeur de la section des unités de recherche

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Affaire suivie par :
Ingrid CHANEFO,
Directrice de la Recherche et des Etudes Doctorales

Objet : Réponse de l'établissement support au rapport d'évaluation de l'unité CRBM – UMR 5237
Réf. : rapport d'évaluation S2PUR150008314

Messieurs

Je tiens à remercier le comité de visite pour la qualité de son rapport d'évaluation concernant l'unité de recherche CRBM-Centre de Recherche de Biochimie Macromoléculaire (UMR 5237), dirigée par Mme Anne DEBANT.

J'ai bien noté les remarques formulées par le comité de visite et veillerai à leur prise en considération par la future direction de cette structure.

En tant que tutelle universitaire de cette unité de recherche, je ne formulerai aucune remarque supplémentaire

Je vous prie d'agréer, Messieurs, l'expression de mes salutations les plus respectueuses.

Le Président de l'Université Montpellier 2,

UNIVERSITE MONTPELLIER 2 SCIENCES ET TECHNIQUES

Michel ROBERT

Pièce(s) jointe(s) :
Relevé des erreurs factuelles à rectifier dans le texte du rapport
Observations générales formulées par le directeur

La Directrice du CRBM

Montpellier, april 25th 2014

Objet: Response to the AERES report on CRBM

We thank the AERES committee for both the time and work that it devoted to our achievements and projects. We thank them for their careful and in depth investigation of our strengths and weaknesses and for the pertinent recommendations they propose.

Comments concerning the Institute as a whole

We are very pleased by the very positive evaluation of our collective achievements and projects. The committee acknowledged the first-rate level of our scientific production.

We appreciate that the review committee has been impressed by the scientific policy that was conducted during the last years. The committee acknowledges the definition by the direction of clear scientific objectives and the profound reorganization that has improved the scientific dynamics of the institute. In this respect, two main points have been pointed out by the committee: i) the recruitment of seven new teams including 3 teams led by foreigners after two international calls reinforcing the major areas of expertise of CRBM and ii) the restructuring of existing teams to focus on the main areas of research.

The committee acknowledged that this very active policy of recruitment and reorganization clearly illustrates the attractiveness of CRBM, and that augures very well for the future. We agree with the committee that specific care should be taken to provide the appropriate conditions for the favorable development of these 7 teams especially in terms of technical support. We are aware of that, and we would like to mention that 3 new teams out of the 4 have already been allocated by the direction a technical support. We are also actively requesting technical positions from our funding bodies.

The committee is confident that the direction will pursue his efforts on focusing on the main domains of expertise to increase international visibility. One first concrete action will be the change of the institute name that does not reflect anymore the new focus of CRBM. We have focused now our research on cell biology as a main tag, and we agree with the committee that we are in a good position to integrate quantitative methods in our research project. In this respect, the presence of the MRI Platform in combination with the link with the IBC (Institut de Biologie Computationelle), and the Functional Proteomic Platform are real assets for CRBM future.

We will do our utmost to live up to the confidence placed in us by the committee and will now act to achieve our high-profile 2015-2019 objectives.

Comments concerning the teams

No comments

Centre de Recherche de Biochimie Macromoléculaire *(CRBM) UMR 5237*

Anne DEBANT, DR CNRS
Directrice du CRBM

Serge Roche, DR INSERM
Directeur-adjoint du CRBM

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