CRCM - Centre de recherche en cancérologie de Marseille

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Centre de Recherche en Cancérologie de Marseille

From the

Université de la Méditerranée

January 2011

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

January 2011

Research Unit

Name of the research unit: Centre de Recherche en Cancérologie de Marseille

Requested label: UMR Inserm/CNRS

N° in the case of renewal

Name of the director: Jean Paul BORG

Members of the review committee

Committee chairman

Ms Jessica ZUCMAN-ROSSI, Université Paris-Descartes, Paris, France

Other committee members

M. Alain EYCHENE, Institut Curie, Orsay, France

Ms Michaela FONTENAY, Université Paris-Descartes, Paris, France

M. Pierre LAURENT-PUIG, Université Paris-Descartes, Paris, France

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M. Carl MANN, Life Sciences Division, CEA, Saclay, France

M. Peter MARYNEN, University of Leuven, Leuven, Belgium

M. Francisco REAL, Spanish National Cancer Research Centre, Madrid, Spain

M. Eric RUBINSTEIN, Université Paris-Sud, Villejuif, France (Inserm CSS)

M. Vincent VILLERET, Université de Lille 1, Lille, France (CoNRS)

Observers

AERES scientific advisor

M. Pierre LEGRAIN

University, School and Research Organization representatives

Ms Ursula HIBNER, CNRS

Ms Chantal LASSERRE, Inserm

M. Pierre CHIAPPETTA, Université de la Méditerranée

Report

1 • Introduction

• Date and execution of the visit

The site visit took place on January 26th to 28th 2011, during 3 days, at Institut Paoli Calmettes. Two weeks before the visit, each committee member had received a report in English including the description of the work performed in the last four years and the proposed projects for all the 17 teams that are part of the present project. Overall, this report contained all the information required by AERES and enabled an efficient preparation of the visit.

The visit opened by a closed-door session to prepare the review. In a public session, the AERES delegate explained the AERES aims and strategy. Then, the future director of CRCM presented the project during 1 hour.

During the 3 days of visit the overall committee participated to the visit:

- each of the 17 team leaders presented their projects in 30-45 minutes followed by 15-30 minutes of discussion.

- The first day, the committee had a 1-hour closed meeting with representatives from the Université de la Méditerranée (including Facultés de Médecine et Pharmacie), the Inserm, the CNRS and the Paoli Calmettes Institute.

- The first day, the committee was split into three parts to meet students and post-doctoral fellows, engineers and technicians, and the researchers with permanent position.

- The second day, the committee had a 1-hour closed meeting with the proposed director and the two proposed deputy directors of the future Centre de Recherche en Cancerologie de Marseille (CRCM).

- At the end of the each day, the committee had a 90 minutes closed-door meeting to evaluate each team and to prepare the report.

- At the end of the third day, the committee discussed the evaluation of the overall CRCM project and prepared the final report.

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

The Centre de Recherche en Cancerologie de Marseille (CRCM, UMR 891) directed by Françoise Birg was created on January 2008 by Inserm with the support of the Université de la Méditerannée and of the Institut Paoli Calmettes (Centre de Lutte Contre le Cancer, IPC). At present, CRCM includes 9 teams located at Institut Paoli Calmettes, seven were endorsed by the Inserm at the creation (including an AVENIR team), 2 junior teams joined CRCM during the last years (Bioinformatics and epigenetic of hematological diseases) whereas an AVENIR team moved to CIML, Marseille Luminy. The main goal of CRCM is to propose a comprehensive and innovative research program in cancer with a continuum from basic and translational to clinical research. Major CRCM programs are the identification and validation of novel therapeutic targets, understanding and manipulation of host-tumor relationship, identification of molecular signatures of tumors and innovative clinical trials linked to onsite fundamental research with a major interest in breast and hematological diseases. CRCM has also a recognized expertise in genomics, cell signaling, protein-protein interaction, immunomonitoring and protein kinases.

The proposed CRCM project corresponds to the association of all the teams already hosted by IPC with (1) the CNRS unit “Instabilité du Génome et Cancérogenèse” (IGC, UPR 3081 CNRS) directed by Robert Fuchs at Institut de Biologie Structurale et Microbiologie, Marseille and (2) the Inserm Unit “Stress Cellulaire” (Inserm U624 located at Marseille Luminy).

The project includes a total of 17 (10 seniors and 7 juniors) teams with common priorities in cancer research sharing core services. A new research building will open late 2011 at IPC, it is planned to host the IGC teams in 2012 whereas Inserm U624 teams will stay at Luminy in a first step, progressively integrating IPC in the next 5 years.

- Management team

CRCM is managed by a director (Françoise Birg) and Jean-Paul Borg is proposed as the future director with two deputy directors, Vincent Geli (IGC, CNRS) and Juan Iovanna (Inserm U624). The director will be assisted by an Executive board composed of the director, the two deputy directors, the IPC general director, the present director and 6 senior group leaders. A management committee will be composed of the present director and the administrative Officer of the CRCM.

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	24	24
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	44	45
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	41	41
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	59	59
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	18	
N6: Number of Ph.D. students (Form 2.7 of the application file)	42	
N7: Number of staff members with a HDR or a similar grade	49	52

2 • Overall appreciation on the research unit

- Summary

The overall scientific level, management and facilities are very good in the three entities (present CRCM, Inserm U624 and IGC) that want to merge. The center that is being proposed is scientifically coherent with the participation of very good and excellent teams. The teams have in general a very good involvement in the national and international networks. By the proposition of enlargement, CRCM has provided evidence for its scientific attractiveness and leadership in Marseille for cancer research. The project was initiated by the different group leaders that want to gather their expertise to increase their scientific cooperation. In this future project, CRCM wants to (1) reinforce its basic research programs by including high level research in the field of DNA repair, genomic instability, DNA replication, telomere biology and epigenetic DNA modification, because all these topics are essential for the comprehensive understanding of the biological mechanism at the origin of cancers but also for better define and target the therapeutical tools to treat cancer and (2) develop a comprehensive program on pancreatic cancer from basic to clinical research.

- Strenghts and opportunities

- CRCM benefit from the important support and hosting by the Institut Paoli-Calmettes that is a private, independent, non-profit cancer center involved in the management of nearly 6,000 new cases of cancer each year. Thus, IPC is one of the largest center for cancer treatment in France. IPC is also an important cancer research center.

The high-quality of the research performed at CRCM is well recognised at the national and international levels, particularly with an outstanding expertise in cell biology (polarity, traffic, etc…), immunology, breast cancer and leukemia.

- Overall, merging with IGC teams and Inserm U624 appears as a positive move which should reinforce already existing interactions between basic and clinical research on the campus. In a 10-years vision, this merging could give the opportunity for the development of an outstanding cancer research center.

- Critical mass in the immediate vicinity, well organized platforms, strong community spirit devoted to cancer, charisma of the future director, all contribute to make the center attractive.

- Strong and long term support of IPC to research in general is the basis and a guarantee of success for the cancer research center that continuously increases in size particularly thanks to the development of new buildings.

- Young investigators, AVENIR or ATIP, hosted in the CRCM or IGC have the opportunity to set up their independent team.

- ## Weaknesses and threats

- Some aspects of the project are immature and should be taken into consideration to guarantee the success of merging CRCM/IGC/Inserm U624. In particular, scientific interactions between the different entities need to be developed prior and after merging. Partners should start without delay joint scientific programs and seminars.

- The new CRCM project needs a full support from all institutions. The success of this project will strongly depend on the extent of CNRS participation and support. As one practical example, there has been much constructive work at IGC during 2011 on setting up advanced optical instrumentation for single-molecule studies with macromolecules, with Dr Mauro Modesti as a driving force; it is absolutely essential not to stop and put in danger this outstanding program of research.

- The increased size of the center needs to better adapt its governance. Space distribution to each team should be clearly stated in a written document approved by all team leaders and the direction. This repartition has to preserve enough space to recruit new groups in the future.

- The committee fully agrees that clinical research is a major aim and achievement for the CRCM. This activity is unique in the center because it takes advantage of both a high level of clinical management and recruitment of patients together with a high level basic and translational research devoted to cancer. However, structuring in teams the translational and clinical research activity should be better defined. Added value of excellent clinicians with a formation in biological research working at IPC should be better enlightened and recognized by maturating an original organization that could accelerate the translation of the scientific findings to clinical applications. Moreover, strengths of the hospital should be better defined and integrated in the research plan, team leaders should clearly show how they want to capitalize on them.

- Considering the quality of the research and some important discoveries performed at CRCM, several CRCM group leaders should better communicate their results at the international level. An important recommendation is to submit and publish their results in highest impact journals, but also increases the number of scientific presentations at international meetings. Therefore, international attractiveness could be reinforced. Arrival of the IGC teams will certainly contribute to that point.

- Keeping Juan Iovanna's team at Luminy could be an obstacle for the development of the common project.

- Bioinformatics/systems biology and sequencing platforms need to be developed at CRCM.

- Recommendations

The committee has suggested several recommendations to prepare the merging in good conditions:

- The committee recommends to increase as of now the scientific relations between the three entities with the organisation of common scientific seminars, dissemination of technical and plateform information, maturation and development of scientific projects, proposal for financial supports of collaborative projects. This is an absolute necessary prerequisite for a successful merger. A precise planning and agenda for merging should be elaborated and submitted by all the partners of the future CRCM.

- Structure of the future center should be better maturated and defined. Taking into account the highly increased number of participating teams, creation of at least two departments is probably necessary to better disseminate the informations and organise the future scientific life of the center. CRCM will have to adapt composition of its SAB to represent sufficiently the new fields of research. The role of SAB will be essential to adapt how the different scientific topics should be further developped in the future CRCM.

- To provide consensual document defining the initial distribution of space and technical support for each group. To precise how the modification and the decision will be taken for the next 4-6 years.

- Size of the executive committee (including only 2 persons) is under-estimated and should be increased.

- Support of all the participating institutions has to be clearly defined. Particularly support of the CNRS is necessary to guarantee the manpower and the specialised instrumentation necessary to the development of the research programs in the teams currently labellized in IGC.

- To try to increase highest profile publications and to encourage participations to international meetings in order to improve international recognition of the researchers.

- To encourage prioritization between the various projects developed in several teams.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	24
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	43
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	1
A4: Number of HDR granted during the past 4 years	9
A5: Number of PhD granted during the past 4 years	52

3 • Specific comments

- Appreciation on the results

An impressive number of publications were published by researchers that participate to the CRCM project, this is the reflect of a high quality and originality of the performed research.

- At present CRCM, during 2006-2010, more than 370 manuscripts were co-authored by CRCM researchers. Among them 20% are publications resulting from a collaboration between two CRCM teams. Among them >60 manuscripts were published in journal with IF>10 (Nature, Nature Genet, NEJM, Cell cycle, Lancet, Blood, PNAS…); >80 manuscripts were published in journals with 5<IF<10 (Cancer Research, Oncogene, Leukemia…).

- At ICG >20 manuscripts were published in journals with IF>10 (including Cell, Nature Cell Biol, EMBO J…) and >10 in journal with 5<IF<10 (NAR, J cell Science…). Among them, most of the papers are co-authored with a team member either at first and/or last position.

- At Inserm U624, more than 130 manuscripts were co-authored by researchers. >10 publications in IF>10 ; >20 publications in journals with 5<IF<10

- An impressive number of collaborations are undertaken by all three partners.

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

Several members of the CRCM, IGC and Inserm U624 have been invited in a large number of national and international meetings. Several researchers received awards and/or PES (prime d'excellence scientifique) PER. The three partners have recruiteded numerous doctoral and post-doctoral fellows during the last 4 years. As an example, at CRCM, 36 students have defended their PhD thesis from 2006-2010 ; 82 students obtained a MASTER 2. Numerous grants have been obtained (ANR, Inca, LNCC, ARC…), several teams have close partneships with biotech companies (Innate Pharma, Ipsogen, Modul Bio, Immunotech). All these points are detailled further team by team. Enlargement proposed in the present project including hosting of young high level teams is the results of an impressive attractiveness of CRCM.

- Appreciation on the management and life of the research unit

The proposed director of the CRCM appears to be well appreciated and respected by his colleagues.

Approximately one third of the trainees are from abroad; there is approximately a 2:1 PhD:postdoc ratio. The students felt that there was an adequate level of scientific activity (seminars, etc) in their groups/units but they might benefit from more interaction between CRCM, Inserm-Luminy and CNRS Unit. Postdocs had prepared the meeting and indicated their desire to be able to apply for their own funds. There was a general concern about being prepared for their future career (ie. being competitive in "concours"). In this context more attention could be paid to the presentation and discussion of results before an audience outside the laboratory. The possibility to attend conferences was also put forward as a point of attention. There was also concern about training on grant writing. The whole group of researchers indicated that – if the merge occurred – it would be important to homogenize criteria for meeting attendance and for other general issues. The staff of ITA from the three merging units felt well supported in terms of formation and preparation of competitive examinations. They raised the issue of the cohabitation of staff with different contracts: CDD, IPC and EPST, and were concerned about the future of staff with temporary position. Finally, the ITA staff of the CRCM was very pleased by the current management of ITA, with a representation at the "conseil de laboratoire" and the existence of an ITA council that participates to some aspects of the management. They wished there had more discussion on the future management mode, and wished that the current system be kept.

Several researchers of CRCM are actively involved in teaching and training both in the field of biology, pharmacy and medicine. CRCM is one of the most important training sites for oncology in France.

- Appreciation on the scientific strategy and the project

Merging of the present CRMC with the IGC and Inserm U624 teams is scientifically highly relevant:

- It has been clearly proven that understanding of DNA repair, genome stability and in general DNA metabolism are important in the cancer field of research classically to better understand initiation and mechanism of malignant transformation but also now for drug development (PPAR inhibitors being a perfect example).

- To develop a successful research in a cancer center, translational and clinical cancer research needs to be continuously nourished by a basic research. Basic researchers will also benefit in the acquisition of knowledge of cancer from the proximity of clinicians and biologists to better translate, if possible, their basic findings.

- Overall, quality of the research performed in the future cancer research should benefit from the reinforcement of the basic research to develop original high-level programs.

The present project is highly supported by the IPC direction, Inserm, University of Méditerranée, IPC SAB (Scientific Advisory Board of Institut Paoli Calmettes, Nov 2010) and the overall researcher community participating to the project.

The unexpected availability of a new building on the Hospital campus in 2012 has triggered a rapid consideration of a geographic merger between the IGC and the Inserm unit 624 at the hospital (IPC).This creation of a larger unit may be of considerable advantage in the long perspective, since it might facilitate the development of a program of translational research, as well as possibly improved national and international funding. However, this project would require a functional and impressive unit that does not exist yet. Thus, an important effort is urgently needed to develop the necessary groundwork for a successful merger, including personal contacts and joint plans. Overall, the objective to construct a competitive cancer research center appears as a high level, original and ambitious project in itself.

4 • Appreciation team by team

Team 01: Molecular Oncology - Daniel BIRNBAUM

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	6	6
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	10	10
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	3	
N6: Number of Ph.D. students (Form 2.7 of the application file)	7	
N7: Number of staff members with a HDR or a similar grade	10	13

- Appreciation on the results

This is a large group that is working on a broad spectrum of projects ranging from the genomic analysis of breast cancer, colon cancer, and haematopoietic malignancies to various aspects of cancer stem cells and cancer cell biology including the role of centrosomal proteins in cancer. The group also provides assistance for two other CRCM groups by running a genomics platform. This is the most prominent team on breast cancer genomics at the French level and they are leading a large prospective project on the inherited genetic basis of colon cancer metastasis by leading a multicenter cooperative group. There is also a more marginal participation in the breast component of the ICGC international project. The group made major contributions to the field of molecular characterisation of hematologic malignancies. In the last 4 years, they have made an important contribution by discovering a new gene mutated in human MDS (myelodysplastic syndrome) and in several types of leukemia.

These results did make optimal use of availability of well documented tumor samples and do have translational relevance. Their work is state-of-the-art but it does not yet push the boundaries beyond this state-of-the-art.

The group has published more than 75 papers with 7 of them in top journals (including one from a large Consortium and two letters to the NEJM). The remaining papers are published in specialized journals.

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

The group participates in several international Consortia and has organized scientific meetings. The citation level indicates the recognition of its visibility at the international level. The seminal contribution by identifying mutations in ASXL1 in leukemia is widely recognized.

- Appreciation on the scientific strategy and the project

The group's proposal covers a wide range of projects ranging from cancer genomics for the search of markers of progression, response to therapy, and risk of metastasis, to the analysis of epigenetic changes and the study of breast cancer stem cells and centrosome biology. The breadth of the projects will be an asset for the future CRCM since this group will be able to establish fruitful interactions with a large number of teams from the center, both basic and clinical.

- Conclusion :

- Excellent technical expertise which renders a good service to the CRCM.

- Very dynamic group involved in a wide variety of projects with translational and basic implications.

- The breadth of the projects may be excessive and some focus might be desirable.

- They should aim at positioning themselves at the top at the international level at least in one of the three tumors that they are working on.

- The group should aim at increasing their competition for EU and international funding.

Team 02 : Cell polarity, cell signalling and cancer - Jean-Paul BORG

- Staff members

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

- Appreciation on the results

The team is focusing its interest on several candidate proteins involved in epithelial cell polarity and their implication during development and carcinogenesis. These include Erbin, previously identified by the group leader as an interactor of ErbB2 TK receptor, the related Scribble and Lano proteins and connected receptors Vangl2 and Ptk7, and the tumor suppressor LKB1 serine/threonine kinase. The functions of these proteins are investigated using a combination of animal models, cell biology, and biochemistry.

Among the recent results obtained by the team :

- the generation of erbin knockout mice, demonstrating the role of Erbin in regulating ErbB2 signaling and myelination of the peripheral nervous system. The identification of novel partners of Erbin (Smad3, Merlin), implicating Erbin in additional intracellular signaling pathways.
- the evidence that Scribble regulates cell migration through the regulation of the PAK kinase. In addition, the team showed that Ptk7, a receptor associated with Scribble, interacts with β-catenin, thereby regulating the Wnt/GSK3/β-catenin signaling pathway.
- the demonstration that the LKB1 complex could function downstream of E-cadherin in tumor suppression: active LKB1/STRAD kinase complexes colocalize with E-cadherin at adherens junctions, suggesting that in polarized epithelial cells, E-cadherin regulates AMPK phosphorylation by controlling the localization of the LKB1 complex.

Of note, to achieve these projects, the team has generated erbin, lano and ptk7 deficient mice strains.

During the evaluation period, the team had an excellent scientific production of 21 original articles, among which 6 with the group leader as last and/or corresponding author in very good journals (IF: 7-10)(Blood; Hum.Mol.Genet.; EMBO rep.; Mol.Cell.Proteomics; Oncogene). In addition, a paper in Current Biology (IF 11) is signed by a staff scientist from the team as first and corresponding author in 2009. The other 13 publications come from internal or external collaborations, some of them in excellent journals (PNAS, Dev.Cell., …).

Of note, the team has filed one patent and 2 PhD defended their thesis (2007 and 2009).

During the evaluation period, the team has been involved in many fruitful collaborations, which resulted in several publications, including articles in PNAS, Developmental Cell and Current Biology.

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

The group leader was frequently invited as speaker in conferences, most of them in France and two abroad, one in Hambourg, Germany (2006) the other in London, UK (2008).
Award: Prix 2010 de La Ligue Contre le Cancer du Var

The team has recruited an Inserm senior researcher (CR1), 6 post-doctoral fellows including 3 foreigners (India, Italy, United Kingdom). Several PhD student from France and abroad are currently trained in the team.

There is a good balance between staff scientists, technicians, post-docs and students.

The team is well funded (labellisation Ligue (LNCC), ANR, INCa, Fondation de France, EU, canceropole PACA). It participates to 2 ANR and two European projects, although not as coordinator.

The group leader has a strong regional and national visibility. He will be the future Director of the CRCM and holds several national administrative and scientific responsabilities, among them:

- scientific co-coordinator of the Marseille Proteomics Platform (MaP) labelled IBISa in 2009.
- Scientific coordinator of the Canceropole PACA and of the "Functional Genomics" axis.
- Member of the Scientific Committee of Conseil Consultatif Régional pour l'Enseignement Supérieur, la Recherche et la Valorisation (Conseil Régional PACA).
- Member of the Scientific Committee of Fondation pour la Recherche Médicale and Président of a Regional Scientific Committee of Association pour la Recherche sur le Cancer.

In addition, the team developped fruitful collaborations with numerous labs in France and USA and the group leader has co-organized 4 scientific meetings in Marseille.

- Appreciation on the scientific strategy and the project

The proposed projects are in the continuity of the past activities of the team on cell polarity proteins involved in cancer development. They are based on the extensive use of the different mouse models developped in the lab, as well as on high quality biochemical and cellular imaging approaches. The proposed studies include :

- The role of Erbin in the development of the mammary gland and in a mouse model of breast cancer.
- The in vivo role of Lano and Scribble in cell migration using mouse knockout models.
- The molecular interactions between the Vangl and Ptk7 receptors and their role in planar cell polarity.
- The characterization of the composition, intracellular localization and dynamic properties of the LKB1 complex.

Pertinent collaborations have been established with different laboratories, to gather the required expertise for each project. Funding of these highly competitive projects is ensured by both national and international grants.

- Conclusion:

— Summary

The team is leaded by an established scientist with clear national visibility. It is dynamic and well-balanced with an optimal combination of permanent researchers, postdocs and students. Its scientific production is very good in terms of quantity and quality. Strong relevance of the questions addressed in respect with the CRCM objectives.

— Strengths and opportunities

The team displays obvious ability to recruit talented young scientists, to raise funds through competitive grant applications, to develop productive collaborations and to maintain a good critical mass. The projects are molecularly well defined and supported by the efficiency in generating mouse models and in developing top-notch experimental approaches.

— Weaknesses and threats

No major weakness or threat. Many distinct projects are being developed, however, which compels the team to tackle a bunch of various signaling pathways, with maybe a risk of dispersal. Lack of invitations in top ranked meetings.

— Recommendations

The team could improve its international visibility.

Team 03 : Signalling, haematopoiesis and mechanisms of oncogenesis – Patrice DUBREUIL

- Staff members

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

- Appreciation on the results

This team (10–12 persons) is leader in the field of (1) functional characterization of genetic alterations of tyrosine kinase receptors (TKR), c-Kit, in cancer (mainly in mastocytosis, melanoma and gastrointestinal tumours), (2) identification of pathways associated with TKR oncogenic signalling and (3) evaluation of TK inhibitors. The project which aims at identifying novel effectors downstream the TKR and at developing new TK inhibitors is in continuity with previous research.

The focus on c-Kit has been good which resulted in several publications on the mechanism of c-Kit activation and signaling in mastocytosis. The output is good for P Dubreuil as a senior author. Scientific productions : P Dubreuil is co-author on 27 publications of rank A including 3 with IF>10, 7 with IF>6 and 4 PlosOne, and including 11 publications with one member of the team as the first or corresponding author.

- 21 scientific communications to national or international congress.
- 4 PhD Thesis between 2004 and 2010

Valorisation of the research: positive results in the translational field in particular in the development of a novel Kit inhibitor, which could be very relevant. The team leader is the co-founder and in charge of the scientific program of AB Science company . He also coordinates a translational activity (tumour genotyping and functional assays) with the Biopathology Department of the Hospital through a Contrat d'interface.

High quality of partnerships: Part of the program is based on an international scientific network on Mastocytosis (AFIRMM: Association Française pour les Initiatives de Recherche sur le Mastocyte et la Mastocytose) since 1999, recognized by the Ministry of Health as a Reference Center CEREMAST (12 publications).

The team is supported by the LNCC since 2001 (label), ANR, INCa and candidates for a new ligue label and a partnership with the Fondation pour la Recherche Médicale (FRM). Partnership with AB Science (OSEO)

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

The team leader attends three conferences as invited speaker. He co-organized meetings in France : CHO, SFFBM, Eurocancer, Canceropole

One CR left the team in 2008/9, one candidate has been presented for recruitment by Inserm in 2010 and will apply again in 2011. One post-doc fellow currently in the UK will be back in 2011 and will apply later for recruitment by Inserm.

The team successfully apply for funding. Two sorts of funding:
- Institutional : 2 ANR (1 PI, 1 partner) ending in 2010, INCa (1PI) ending in 2010, INCa (partner) ending in 2011
- Private : LNCC (label), OSEO (AB Science)

Applications in 2011: LNCC (label), FRM

The team is member of an international network on mastocytosis recognized as a National Reference Center and has stable collaboration with several teams in France in Necker hospital, Toulouse, IGR, I. Curie and at C3M in Nice.

The research activity leads to delineate a molecular distinction between c-Kit mutations in mastocytosis affecting adults (TK domain mutations) and children (extracellular domain mutations). A c-Kit TK inhibitor, masitinib has been successfully used in human phase II clinical trials and entered phase III trials in aggressive mastocytosis, GIST and pancreatic carcinomas. The drug has been registered by EMEA for veterinary use.

- Appreciation on the scientific strategy and the project

The relevance of the 4-year program is based on the requirement for new TK inhibitors aiming at characterisation of off target interactions. The feasability is supported by facilities in the research center (animal models), "centre de ressources biologiques" for AML investigations and active collaborations with AB Science for pharmacology of TK inhibitors.

The part 1 of the project is the continuation of previous work, very hypothesis-driven and well focused at the same time with high translational content. The specific issues are approached with state of the art methodology. Recruitment of a full-time researcher could help at addressing the specific aims of this part of the project.

The part 2 entitled " caracterization of kinases required for leukemic cell proliferation" aims at identifying novel therapeutic targets in leukemia using a siRNA screens in various leukemia cell lines, probably meyloid leukemia cell lines. The applicant team does not propose a validation plan for potential targets that will emerge from this screen in human samples. However, the team already focuses on the role of Fer and Fes kinases, which are known downstream targets of Kit anf Flt3, in leukemia and solid tumors. The subaims of the Fer/Fes kinase project encompass their role as oncogene, their function at the cytoskeletal level, their potential alterations of activity or sequence in a variety of malignancies and the establishment fo a fes/fer deficient mouse model. Some important informations are lacking for assessing the feasability of the translational part of the project : for instance, which are the tumor cell lines in which Fes/Fer mutations have been found? Why does the applicant chose melanoma, colorectal carcinoma and lung cancer ?

The part 3 aims at evaluating kinase and HDAC inhibitors in collaboration with AB Science company. A good interaction is definitively of interest, even if some of the projects are more suitable to be conducted in the company (HDAC inhibitors) rather than the research group since this group focuses on kinases and kinase signaling. In the study of dog mast cell tumors (202 dogs have been treated with masitinib with only 25% response rate), it is hypothesized that dogs without response to masitinib will have another kinase mutation (not Kit). A very interesting project is initiated to identify these mutations. The identification of off-target effects of masitinib is a straight forward approach and fits with the studies of the lab. Lastly, the study of epigenetic modifiers (possible in relation with kinase inhibitors) appears to go too far away from the research focus and lacks a good scientific rationale for developing the covalently linked masitinib-HDAC inhibitor.

Two cutting edge projects:
One is the investigation of theranostic factor (predictive of the response to masitinib) in dog mast cell tumors in collaboration with a CNRS team in Rennes.
The second is a partnership with AB Science which aims at designing inhibitors with a dual specificity of kinase inhibitor and epigenetic modifiers.

- Conclusion :

— Summary

This team is implicated in establishing the relationship between genotype and phenotype in diverse c-Kit mutated tumors by investigating specific signaling pathways and also in developing personalized therapeutic strategies using small inhibitory molecules. Past research has produced numerous high quality scientific publications leading to a significant contribution to the knowledge and to an international visibility.

Basic and translational researches are conducted, together with active collaboration with a biotech for development of inhibitory small molecules.

The scientific program is good although some points need to be refined or clarified.

— Strengths and opportunities

The strengths and opportunities of this team are the coexistence of basic and translational research efficiently supported by an international network (AFIRMM), a pharmaceutical company (AB Science) and the facilities (animal house, IPC sequencing platform, proteomic platform).

— Weaknesses and threats

The number of full-time researchers is low, considering the number of important projects.

— Recommendations

This team presents a good scientific program with extremely promising results in the therapeutic field and could benefit from the recruitment of a full time researcher.

Team 04 : Tumour cell motility - Ali BADACHE

- Staff members

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

- Appreciation on the results

The team focuses on the mechanisms whereby the tyrosine kinase receptor ErB2 regulates cell motility. The project has been based so far on state of the art cell biology approaches, which have allowed uncovering new molecular links between ErB2 and the microtubule network. Since its creation as an Inserm AVENIR team in 2005, the research is mainly based on a seminal discovery from the group leader, that Mediator of ErbB2-driven cell Motility (Memo), a protein of unknown function with no homology with others, is an effector of activated ErbB2 receptor that controls cell migration by relaying extracellular chemotactic signals to the microtubule cytoskeleton (Nat.Cell Biol. 2004). During the last quadrenial, the team reported several interesting observations as to the structure and the role of this protein in microtubule dynamics and cell motility. They recently showed that the ErbB2-Nemo pathway controls microtubule capture and stabilization by recruiting the spectraplakin ACF7 to the plasma membrane at the leading edge of the cell via GSK3 and APC tumor suppressor (PNAS 2011).

During the evaluation period, the team published an invited review and three original articles. The scientific production could be considered as excellent in regard to the size of the team, with two major publications in excellent journals (J.Cell.Biol., 2008; PNAS, 2010) with the group leader as last and corresponding author and with the same PhD student from the team as first author. In agreement with its small size, the team privileges publication in high-ranking journals rather than the number of publications.

Of note, no strong interactions with other CRCM teams are described.

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

The team had several invitations to meetings in France, no invitations to international conferences, nevertheless two selected oral communications in international conferences (US and UK).

During the last quadrenial, 2 PhD students, 4 M2 students and 2 post-Docs have been recruited. From this list only one of the 2 PhD students has published as first author (JCB 2008 ; PNAS 2010).

The PI is the scientific manager of the imaging facility at the CRCM. The team was supported by an Avenir grant from Inserm between 2005 and 2008. During the evaluation period, the team also obtained support from Fondation de France, ARC and INCa.

Appropriate collaborations have been established with different laboratories.

- Appreciation on the scientific strategy and the project

The future projects of the team aim at defining the underlying molecular and cellular mechanisms by which ErbB2 regulates cell motility, using cellular imaging, structural analyses and proteomics. This includes the characterization of the ErbB2-Memo complex at the molecular level, and the respective contribution of the different Dia-related Formins downstream of Memo in ErbB2-driven cell motility. In addition the team proposes to identify new effectors of cell motility using a proteomic approach in cells depleted or not in Memo protein.

The proposed projects are highly interesting, well focused and described. They will combine hypothesis-driven approaches, as well as proteomic analysis of discrete cellular structures. This second approach is made possible by the arrival in the team of a researcher with a strong expertise in tubulin proteomics. The equipment and technologies appear already set up and available and appropriate collaborations have been established with different laboratories. The PI is the scientific manager of the imaging facility. However, the use of proteomics for addressing the particular structures of interest appears technically challenging and its feasibility is not clear.

- Conclusion:

— Summary

The team is promising and its projects are at the forefront of cell migration studies. The PI was able to publish his results in very good journals, indicating an appreciable ability to valorize his research. In agreement with its small size, the team privileges publication in high-ranking journals rather than the number of publications.

— Strengths and opportunities

- Original cutting edge projects and excellent scientific production of the PI.

- Very convincing oral presentation in front of the visiting committee.

- Strong skills in cellular imaging.

— Weaknesses and threats

- Despite an Avenir support from Inserm (2005-2008), the team did not succeed until now in reaching the critical manpower required for securing the projects. However, the expected arrival of a new Inserm staff scientist in the team should help reinforcing the team. The projects are ambitious but maybe too numerous with regards to the small size of the team. The existence of funding for the future recruitment of post-docs and/or technicians is not mentioned.

- The proteomic analysis will depend on the ability to purify discrete cellular structures, the feasability of which is not clear.

- Lack of strong interactions with other teams.

— Recommendations

The team is promising but needs to consolidate by increasing the manpower and the number of Post-Docs and PhD students publications. The PI should take benefit from his excellent scientific production to apply to international calls for proposals.

Team 05 : Adhesion molecules in host-tumour interaction - Michel AURRAND-LIONS

- Staff members

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

- Appreciation on the results

The team is a Inserm Avenir Team created in 2007 and renewed in 2010. The team leader was recruited at Inserm in 2010 at the CR1 level.

The team focuses on the interaction of tumour cells with cells of the microenvironment, through the study of relatively poorly studied molecules called JAM-B and JAM-C that interact with one another. A number of original observations have been made, showing the contribution of this molecular system in hematopoietic stem cell homing as well as in the immune response.

There are not yet publications of the team for the work developed at the CRCM. However, 3 years is quite short for producing high impact publications, especially if animal models had to be set up. The group leader has participated to 21 publications in good journals since 2006, including one in Science.

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

The team leader is involved in a number of fruitful collaborations as judged by his publication record, attesting of international recognition. However he lacks invitations in international meetings. His ability to rise competitive funding is attested by the obtainment of an AVENIR fellowship as well as fellowships for 2 postdocs. A number of local collaborations are being set up.

- Appreciation on the scientific strategy and the project

The project is partially in continuity of the in vivo results already obtained. New perspectives are also developed based on a number of original observations, including the identification of a new receptor and a new intracellular partner regulating the surface expression of JAM-C.

- Conclusion :

The team is new but is leaded by an established scientist. There are not yet publications originating from the studies developed in Marseille. The team has collected many original interesting results that will certainly be published quite soon.

Strong relevance of the questions addressed in respect with the CRCM objectives.

— Strengths and opportunities

Strong expertise of the team leader in adequation with the project.

Original animal models

Ability to recruit postdocs

— Weaknesses and threats

The team has not published yet since it was created in 2007, and its funding is not secure.

— Recommendations

The rapid publication of their results in high impact journals will be critical for the future of the team, in terms of attraction of students and ability to obtain grants.

Team 06 : Epigenetic control of normal and pathological haematopoiesis – Estelle DUPREZ

- Staff members

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

- Appreciation on the results

This team focuses on the epigenetic control of normal and pathological hematopoiesis and investigates the regulation of the transcription repression by the polycomb group (PcG). Studies of the mechanisms of PcG targeting at chromatin level should help to understand how the hematopoietic stem cell is maintained or forced into differentiation. The team leader has extensive experience in this field and has previously reported a new mechanism of PcG recruitment to the chromatin implicating the transcription factor PLZF. Recent advances by genomic approach demonstrate that several regulators of PcG could be inactivated by acquired somatic mutations in myeloid or lymphoid malignancies. Thus, the relevance and originality of the project is indubitable. Two MD have joined the team and will contribute to translational research in the field.

The team leader has two excellent publications as co-author in Cell and as senior author in Gene & Dev in 2009 before starting the new team at CRCM in 2010. She is joined by 1 PU-PH and 1 PH whose publication list is not provided.

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

The team leader has been invited to give a talk at Pasteur Institute

This team is under development and was joined by three permanent staff (1 PU-PH, 1 PH, 1 THQ). The team leader applied for a grant (ARC and LNCC) to recruit one post-doc fellow in 2011.

The team leader successfully apply for funding from ARC (2x before starting the team, 1 after), Association Laurette Fugain, and Fondation pour la Recherche Médicale.

The team leader demonstrates her good integration in the CRCM by establishing an in situ collaboration with team 15 to test the effects of new compounds supposed to be epigenetic modulators in the cellular systems set up by this team, and with team 03 to evaluate the importance of PcG in mast cell differentiation.

For next generation sequencing, a core facility that does not exist in the research center, the team leader has established collaboration with the Cancer Science Institute in Singapore.

Until 2010, the team mentions one manuscript in preparation reporting by a genome-wide PLZF CHIP-onChip approach that PLZF target genes in myeloid cells are also PcG targets.

- Appreciation on the scientific strategy and the project:

The project aims at understanding epigenetic regulation of normal and malignant hematopoietic stem cell (HSC) and myeloid progenitors. The research will focus on the role and concerted action of PLZF and PcG in normal hematopoiesis and malignancies based on previous studied from her group and others. This excellent project is technically very challenging, but it may have significant impact in understanding leukemia development and may lead to novel drug schemes for therapy.

While the relevance of the project is indubitable, it a very challenging program for a small group in a very competitive field. The feasability will be better set up if a post-doc fellow is recruited (a post-doc application has been sent to ARC and LNCC).

However, technical difficulties are significant, for instance Chip-seq in rare murine HSC, MPP and myeloid cells sorted on 6-7 color-FACS and gene transfer for loss of function/gain of function studies through viral vectors in HSC. No back-up strategies (KO/transgenic mice) are proposed.

Projects include a description of PLZF target genes in acute myeloid leukemia blasts. However, their role in leukemogenesis is not yet addressed and may require to go back to mouse model.

As suggested in one publication, PLZF could be implicated in the regulation of stem cell mobilization. Addressing this question may require the development of dedicated cell systems and should be based on external collaboration.

- Conclusion :

— Summary

This new team aims at studying the epigenetic control of normal and pathological hematopoiesis by the investigation of the role of the PLZF transcription factor in the recruitment and function of Polycomb repressive group. This question will be addressed both in normal hematopoietc stem cell (murine) and in human leukemic cells. This is of particular relevance because of recurrent mutations of PcG regulatory proteins in human hematological malignancies. Four basic research and one translational research projects are proposed.

— Strengths and opportunities

Excellent project, novelty and enthousiasm

— Weaknesses and threats

The team is lacking a full-time researcher for achievement of a program in a very competitive field. One post doc fellow is being recruited in 2011.

— Recommendations

The excellent project could be improved by an effort of structuration on 2 or 3 main points (for instance items I, II and III). The implication of each member of the team in these different projects has to be precised for better evaluation of the feasability. An application for recruiting a second post-doc fellow in 2012 should be useful.

Team 07 : PDZ scaffold proteins and phosphoinositides in cell signalling and oncogenesis - Pascale ZIMMERMANN

- Staff members

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

- Appreciation on the results

The team leader has been recruited at Inserm in 2010 as a DR2, and is expected to join the CRCM in 2011 to create a new group "PDZ scaffold proteins and phosphoinositides in cell signaling". She has previously worked at the KU Leuven in Belgium (research professor since 2002, full-time since 2006), where she was group leader (Laboratory for signal integration in cell fate decision).

The team focuses on the biology of PDZ proteins. The team leader has made substantial advances in the knowledge of two of these proteins, syntenin 1 and 2, by demonstrating an interaction of the PDZ domain of these molecules with PIP2, either at the plasma membrane for syntenin-1, or in the nucleus for syntenin-2. The team leader has published as senior author since 2005 in high impact journals such as Dev Cell, EMBO J and MBC. She is also co author of a dozen of scientific papers in good journals.

Her group investigates scaffold proteins that contain PDZ domains. These domains are important interaction modules that control a plethora of signaling pathways deregulated in cancer and metastasis. Using the syntenin PDZ proteins, her team has made substantial advances. Firstly, they have established that PDZ domains can interact with phosphoinositides (PIPs) and that these interactions are functionally relevant in different contexts. They showed for example that syntenin-1/PIP2 interaction mediates the plasma membrane recycling of its PDZ-peptide ligands, the syndecans. They also showed that the PDZ domain of syntenin-1 interacts with some Frizzled Wnt receptors and controls non-canonical Wnt signaling. In addition, they demonstrated an unexpected nuclear localization of syntenin-2, where it binds to nuclear PIP2 in nucleoli and nuclear speckles and controls subnuclear PIP2 organization.

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

The international recognition of the team leader is assessed from her involvement in a number of fruitful international collaborations, the number of oral interventions in international meetings, as well as the organization of a Gordon conference to be held in 2011. She has authored a review in Current Opinion in Cell Biology. She has already developed a number of collaborations with other CRCM teams. In addition she was the recipient of a EMBO young investigator award (2008-2010).

- Appreciation on the scientific strategy and the project

The project is original, based on a substantial amount of unpublished data, and at the forefront of the research in PDZ domain proteins. The three aims of the projects are: 1,- to unravel how PDZs integrate peptide and PIPs interaction; 2-, to analyze the role of PDZ-PIP interactions in the nucleus. 3-, to analyze the importance of the syntenin-1 endocytic pathway in cancer.

- Conclusion :

— Summary

An original and relevant project led by a renowned scientist, leader in her field.

— Strengths and opportunities

Quality and originality of the project

The team leader is a leading scientist in the field of syntenins.

Local and international collaborations

— Weaknesses and threats

Although the team leader is experienced, she has to build a new group in Marseille which may temporary hamper her scientific production. In addition, she keeps the direction of her team in Belgium, devoting 10% of her time to her Belgium activities. Although this may be seen as an opportunity, it may not be easy to manage the two labs, in term of time sharing and repartition of the projects, including the management of ongoing infrastructures at the KU Leuven (live imaging, biacore facilities).

— Recommendations

Use the upcoming months to refine the strategy of implementing the new team in Marseille.

Team 08 : Cell stress - Juan Iovanna

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	7	7
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	7	7
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	7	
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	9	
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2	
N6: Number of Ph.D. students (Form 2.7 of the application file)	11	
N7: Number of staff members with a HDR or a similar grade	11	

- Appreciation on the results

This group is the second largest of all in the CRCM. The past work has been carried out at the campus of Luminy. The group has a very strong tradition working on pancreatic adenocarcinoma and the cellular response to stress. More recently, a prostate cancer project was added. The activities range from basic to more translational. This team has identified a significant number of novel proteins involved in the stress response whose function is being analyzed. In addition, there are other projects related to pancreatic cancer genomics, cancer-stroma interactions, and clinical applications. The group has published more than 130 papers (with the updated information) and approximately 10% of them are in top journals; some of these are collaborations with other groups. The remaining papers are published in journals of variable quality. The group has also established 5 patents and 2 of them are already licensed. Overall, the work is of high quality.

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

J. Iovanna is internationally recognized in the domain of pancreatic cancer biology. In addition he has a strong track record of excellent international collaborations as well as many national ones, including work with a local group of chemists to develop novel therapeutic strategies. The group has acted as a node of attraction for pancreatic cancer research in the Marseille area and has built the basis for a very strong programme of translational research in this tumor.

- Appreciation on the scientific strategy and the project

The team has identified novel, original, proteins involved in the stress response and has developed a number of other innovative ideas. The current project is based on this work and ranges from basic pancreatic cancer biology to the analysis of their role using mouse models and to clinical exploitation (biomarkers of aggressiveness, predictors of response to therapy). To these aims, the group leader has gathered a multidisciplinary group of researchers including clinical partners. In the next 5 years, they should be able to establish the significance of much of the groundwork that has been carried out.

- Conclusion :

– High quality group with original work and a large number of publications, including some in top journals.

– It would be desirable that an effort is made to increase the median level of publications.

– The project may be too spread out and some focusing might help to make the group more competitive.

– The group should be commended for their effort on translational research and it is encouraged that they consider the possibility of somehow joining or interacting with the ICGC pancreatic cancer projects.

– It is recommended that the group applies for more international funds.

Team 09 : Tolerance to DNA lesions - Robert FUCHS

- Staff members

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

- Appreciation on the results

Robert Fuchs has a long-standing interest in mutagenesis, translesional DNA synthesis (TLS), DNA damage tolerance mechanisms, and in DNA repair. He has made important contributions to these fields over nearly 30 years and his work is internationally recognized. His team masters both in vivo and in vitro approaches. Most of his work has involved these processes in E. coli, but over the last five year period he has increasingly been using yeast models and mammalian cells. This last five year period has been particularly productive with 4 high-impact papers (2 EMBO J. and 2 PNAS) and 7 more in very good specialized journals (DNA Repair, Nucleic Acids Research, Genetics). Furthermore, Fuchs has contributed to several papers published by collaborating laboratories, including a 2009 Cell paper published by Pierre-Henri Gaillard in the same research Unit.

Fuchs continues to produce highly relevant, original and influential research in the field of mutagenesis by translesion DNA synthesis. This work is performed with human enzymes as well as with yeast and bacterial model systems. In E. coli, the specialized DNA polymerases for translesion synthesis, Pol IV and Pol V, have been characterized with regard to replication specificity at sites of damage (Fuchs is the original discoverer of Pol IV). Similar studies have been performed in parallel with the eukaryotic enzyme Pol eta from fission yeast, leading to increased mechanistic understanding of potentially mutagenic translesion DNA synthesis. The involvement of ubiquitination and poly ubiquitination of the replication factor PCNA has been shown to be crucial for efficient translesion DNA synthesis (collaboration with Alan Lehmann, UK). This is a competitive research area, but Fuchs has made major recent contributions that are well recognized internationally.

Another novel result from Fuchs is the finding that altered regulation of precursor synthesis with increased levels of deoxynucleoside triphosphates greatly facilitates subsequent translesion DNA synthesis. There are clearly multiple strategies to allow for translesion synthesis with reduced accompanying mutagenesis, and Fuchs is an international leader in this intriguing area.

Yet another recent investigation by Fuchs of considerable value concerns the puzzling alkyltransferase–like genes that,in several organisms, contains a single site mutation that prevents the protein from acting as an alkyltransferase in DNA repair. Fuchs and co-workers have now shown that this AlkB-like protein binds to alkylated sites in DNA and greatly facilitates their correction by nucleotide excision-repair, and simultaneously prevents attack on these sites by the mismatch repair system which would have a toxic effect in these circumstances (collaboration with team 11).

The Fuchs team has engaged in several fruitful collaborations with the Prakash lab in the US, Alan Lehmann's lab in England, the Cordonnier lab in Strasbourg, and the teams 11 and 12 of this Unit.

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

Robert Fuchs is DRCE at the CNRS and was director of a CNRS UPR unit. He was elected to EMBO in 2006, was invited to give the Severo Ochoa Memorial lecture in Madrid in 2008, and was an Invited Professor at NAIST in Japan in 2009. He has been an invited speaker at 23 international meetings. He was chairman of the 2006 Gordon Research Conference on DNA damage, mutation, and cancer in Ventura, California, and he has participated in the organization of 5 other international meetings on DNA repair and mutagenesis.

The Fuchs' team is composed of a CR2-CNRS research scientist, 2 IR2-CNRS, and 1 IE-CNRS, as well as two postdoctoral fellows. The team would certainly benefit from the recruitment of one or two doctoral students.

The team was funded in France by INCA and the ANR, and they received international funding from the CEFIC (European Chemical Industry Council) and the NIH (co-PI). Finally, the Fuchs team was selected for funding as an Equipe Labellisée of the French League for Cancer Research in 2010.

With regard to recruitment of junior group leaders to the Unit (Instabilité du Génome et Cancérogenèse) since its inception in 2006, Fuchs has done a good job, attracting the leaders of present teams 11 and 12. Their research interests fit well within the Unit and they have gotten off to a good start. The on-going attempt to broaden the profile of the Unit by recruitment abroad deserves support.

- Appreciation on the scientific strategy and the project

Since 2006, the Unit continues and extends the work done previously by Dr Fuchs in Strasbourg on mechanisms of mutagenesis and translesion DNA synthesis. This is an excellent long-term project with high relevance to cancer research.

Two ambitious new projects are proposed over the next four-year period. The first involves a new method for efficiently integrating in the E. coli chromosome a plasmid carrying a single, chemically and positionally defined DNA lesion and studying how the bacterial cell is able to deal with this lesion in terms of induced lethality or repair by translesion synthesis or damage avoidance pathways. No one has yet been able to follow the fate of defined individual lesions in vivo, so this project could produce revolutionary new results in this field. Preliminary results suggest that this approach is feasible.

The second new project involves the identification of DNA damage associated proteins. The team proposes transfecting human cells with plasmids containing defined DNA lesions and then re-purifying the plasmids with associated proteins that may specifically recognize the lesions. A novel technology for affinity purifying plasmid chromatin has been developed for this project and a patent application has been deposited. This approach will require preparing large amounts of plasmid DNA and transiently transfecting a very large number of cells in order to obtain sufficient levels of proteins for identification by mass spectrometry. It is not yet clear whether or not this approach is more likely to identify proteins binding specific DNA lesions compared to the simpler approach of isolating proteins from nuclei that bind specific DNA lesions in vitro. However, an advantage of the proposed approach is that it may allow access to proteins that are recruited to DNA lesions only during S phase by blocked DNA replication forks.

- Conclusion:

  - Summary

The Fuchs team in Marseille is impressive and has made remarkable progress since its move from Strasbourg in 2006.

The Fuchs team is internationally recognized for their long-standing contributions to the field of mutagenesis and DNA repair. They have an excellent scientific productivity, especially given the rather modest size of the team. Furthermore, the team is developing innovative new approaches to surmount technological obstacles in the field.

— Strengths and opportunities

The Fuchs team has an enduring and in depth experience in the fields of mutagenesis and DNA repair. They have developed several fruitful collaborations in France and abroad. Their new system for targeting defined lesions into the E. coli chromosome could put them in a unique position to study how cells deal with these lesions.

There appears to be a good possibility to create one of the best-known international research centres for Genome Instability and Mutagenesis in Marseille.

— Weaknesses and threats

The team is composed of a solid core of permanent scientists, but they are of modest size and are working in parallel on different pathways in E. coli, S. cerevisiae, S. pombe, and mammalian cells. There is thus some risk of over-dispersion of their research efforts. However, it is noted that they have nevertheless managed to be very successful in these efforts thanks to a productive series of collaborations, and Dr. Fuchs mentioned that they would be concentrating their efforts in the near future on the E. coli and mammalian projects.

An upcoming problem relates to the age of Dr Fuchs (63 years). He should be given the opportunity to continue his ground-breaking research work over the next 4-5 year period of the new Research Unit. A former doctoral student and recently recruited CR2 seems well placed to continue this important research effort on mutagenesis and translesion DNA synthesis in the future, possibly in collaboration with Fuchs in an emeritus position.

— Recommendations

The committee fully supports the innovative new research approaches engaged by the Fuchs' team. The team could benefit from recruiting one or two doctoral students. The team should continue their efforts to increase European funding. Be wary of possible dispersion of efforts due to the abundance of model organisms studied in parallel.

Team 10 : Tolerance, senescence and DNA damage - Vincent GÉLI

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	6	6
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

Vincent Géli directs an internationally recognized team working on telomeres, chromatin, and DNA checkpoints in the model organism Saccharomyces cerevisiae. The last four-year period has been particularly productive for this team, and the number of permanent and temporary research personnel has also increased significantly over this period. The team published two very high impact papers in Nature Cell Biology in 2009 on mechanisms of senescence induced by telomere loss in budding yeast in a productive collaboration with the Gilson and Lisby labs. Another major publication concerned the description of distinct mechanisms for replication of the leading and lagging telomere strands that was published in Molecular Cell in 2010. They also collaborated with the Gilson lab on important publications on yeast telomere biology that were published in Nature Structural and Molecular Biology and EMBO Journal in 2006. Their work on the SET1 H3-K4-methyl-transferase complex has been equally productive in collaborations with the Dargemont lab (Nature Cell Biology in 2008), or on its role in targeting meiotic DNA double-strand DNA breaks in collaboration with the Nicolas lab (EMBO J. 2009). They also published significant structure and function analyses of the complex (J. Mol. Biol. 2006 and J. Biol. Chem. 2006). Finally, Géli published a high-profile review on telomere replication in Nature Reviews in Molecular and Cellular Biology, attesting to its recognized leadership in this field.

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

Vincent Géli has succeeded in constituting a large research team composed of 5 CR1-CNRS research scientists, 1 University Professor, a technician (IE-CNRS), two postdoctoral fellows, and two doctoral students. Their current funding will also allow them to recruit at least one more postdoctoral fellow and doctoral student in 2011. The significant size of this team gives them a great research potential. The team has been very successful in obtaining funding with three ANR grants, two INCA grants, and selection as an Equipe Labellisée of the French League for Cancer Research.

Vincent Géli has participated in the organization of 2 national meetings on Replication, Recombination and Repair (2007 and 2009), the organization of the French yeast meeting (2008), and the organization of an EMBO conference meeting on Telomeres and the DNA damage response in Marseille in 2010. He has been an invited speaker at 11 international meetings. He also has had important scientific evaluation positions as President of the Commission on Tumor Genetics of the French Association for Cancer Research and as a nominated member of the Inserm CSS2 commission.

Vincent Géli has established highly productive collaborations with Nice and Copenhagen labs on telomeres, with two labs in Paris on Set1. He has also collaborated with a lab in Sevilla, Spain on characterizing the toxic effects due to the accumulation of excess histones in yeast.

- Appreciation on the scientific strategy and the project

Over the next four year period, the Géli team plans to continue its projects in budding yeast involving telomere biology and replicative senescence, and the characterization of the Set1 H3-K4-methyltransferase.

In the telomere area, they have found that septin mutants undergo accelerated senescence upon loss of telomerase activity and they are studying the molecular basis for this phenotype. Based on this observation, they are also considering the possibility of searching for chemical inhibitors of human septins. This possibility seems a little premature until more is known of the molecular basis of the yeast phenotype. A second project involves testing whether the relocalization of eroded telomeres to nuclear pore complexes might favor homologous recombination mechanisms that can maintain telomere sequences. They would also like to study mechanisms that influence either telomere addition or homologous recombination at chromosome ends. Furthermore, they plan to initiate a project involving the mechanism of telomere recruitment in S. pombe, since this yeast has telomere binding proteins that are more similar to the human homologs. Concerning the Set1 complex, they plan to continue their productive collaboration with the Dargemont lab on the role of the Swd2 subunit on transcription and DNA damage. They also plan to further study how the complex stimulates meiotic DNA double-strand break formation. Finally, their genetic studies of the RRM3 helicase, implicated in telomere metabolism, has led them to an observation of a possible role for this helicase in sister chromatid cohesion that they are currently characterizing.

These projects mainly represent the logical continuation of the highly successful projects that were engaged in over the last four-year period. The telomere and Set1 projects are not highly related, but they are both implicated in distinct aspects of genome stability. The large size of the current research team makes it reasonable to pursue these projects in parallel.

- Conclusion :

— Summary

Vincent Géli has succeeded in creating a large research team with many productive collaborations with leading teams working on telomeres, chromatin, and DNA damage checkpoints in France and abroad. They have had an exceptionally productive four year period with several publications in high profile journals. This work has established them as one of the leading international teams in yeast telomere and chromatin biology.

— Strengths and opportunities

The five CR1 scientists and a good level recruitment of postdoctoral fellows and doctoral students makes this a highly competitive team with excellent proven experience in yeast telomeres, chromatin, and DNA damage checkpoints. Yeast remains an extremely powerful model organism to investigate these areas. A long-term move to the CRCM might give them new opportunities to consider investigating mammalian systems and links to cancer in the future.

— Weaknesses and threats

International funding could be increased.

— Recommendations

Further develop international funding, in particular from European Union networks and the European Research Council. Begin planning links to mammalian systems and cancer in the future.

Team 11: Mechanisms of DNA double strand break repair system: homologous recombination and NHEJ - Mauro MODESTI

- Staff members

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

- Appreciation on the results

Mauro Modesti was recruited to the CNRS with a DR2 position in October 2009 from a staff scientist position at the Erasmus Medical Center in the Netherlands. He studies DNA double-strand break repair by biochemical, cellular, and cutting-edge biophysical approaches. He was first author of a high impact paper in Molecular Cell in 2007 describing a role for RAD51AP1 (Rad51 Associated protein) in stimulating joint molecule formation during Rad51-mediated homologous recombination in human cells. He has also been co-author of at least 11 other excellent publications including a 2009 Nature paper that used optical tweezer technology and single-molecule fluorescence microscopy to study parameters affecting the dissociation of Rad51 from ss DNA fibers. His principal collaborators over the last four years have included the Kanaar and Wuite labs in the Netherlands, and Murray Junop's crystallography group at McMaster University in Canada.

A particular strength is Modesti's expertise in single-molecule studies by fluorescence microscopy of DNA complexed with relevant repair/recombination proteins. This will be an important complement to the more biochemical studies performed by other members of the Marseilles unit.

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

In the short two year period since taking up his position in France, Mauro Modesti has succeeded in recruiting a postdoctoral fellow, creating new collaborations with teams in Marseille and elsewhere in France, and in obtaining some funding for his research. In particular, he has received funding from the Association for International Cancer Research (AICR), the French Association for Cancer Research, the Conseil Régional des Bouches du Rhône, he participates in an INCA project, and he is coordinator of an interdisciplinary ANR project called Radorder. His new collaborators include the Fresnel Institute to implement advanced optical techniques to study Rad51-ss DNA filaments, and the IPBS in Toulouse to search for small molecule inhibitors of DNA ligase 4 complexes.

The team leader was an invited speaker at 2 international and 2 national meetings.

- Appreciation on the scientific strategy and the project

Over the next four-year period, the team leader has wisely chosen to focus his efforts on a few key areas of DNA double-strand break repair that he has successfully worked on over the last 4 year period. An initial project funded by the AICR involves continued investigation of how Rad51AP1 participates in late stages of homologous recombination. A second project involves an interdisciplinary project funded by the ANR (RADORDER project) to further study RAD51-ss DNA filaments by cutting edge fluorescent polarization-anisotropy and FRET techniques on single molecules. An extension of this project involves real-time visualization of the dynamic interactions between ss DNA binding proteins and recombinases on single DNA molecules. Finally, a new project involves a search for small molecule inhibitors of DNA ligase 4 complexes.

- Conclusion :

— Summary

The group leader has proven experience in applying biochemical, cellular, and cutting edge biophysical approaches to the study of DNA double-strand break repair. He has very successfully launched his independent research program in France by obtaining competitive funding from regional, national, and international sources, and by adding new collaborative projects in France to his pre-existing extensive collaborations in the Netherlands and with an expert crystallography group in Canada.

This highly talented and productive scientist will be an important complement to the other members of the Marseille group, especially thanks to his expertise in single-molecule studies.

— Strengths and opportunities

The group leader has proven his ability to participate in interdisciplinary collaborations and to use advanced biophysical approaches to study DSB repair pathways. These should put him in an excellent position to elucidate new levels of molecular detail on the mechanisms of these genome stability pathways.

— Weaknesses and threats

Starting a new lab from scratch in a foreign country for a mid-career investigator carries some risks and necessarily involves some delays as the new lab is established. We are impressed with the speed that the team leader had funding, new collaborators, and new personnel for his lab in France.

— Recommendations

To continue the efforts with further recruitment of postdoctoral fellows and doctoral students. Interdisciplinary approaches and cutting edge technology development are highly appreciated and should give good opportunities to present scientists for permanent positions to this group.

Team 12 : Control of structure specific endonuclease and genome stability - Pierre-Henri GAILLARD

- Staff members

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

- Appreciation on the results

Pierre-Henri Gaillard is an excellent young scientist in the field of recombination mechanisms, with emphasis on the characterization of structure-specific endonucleases. After thesis work at the Curie Institute on chromatin and DNA repair, he did a first postdoc at the ICRF-London on the biochemistry of NER and a second postdoc at the Scripps Research Institute where he started studying structure-specific nucleases in S. pombe. In 2006, he was recruited to the CNRS with a CR1 position and he was selected by the CNRS-ATIP program to start his own research group on the subject in France. He has apparently had some difficulty in getting his research program off the ground, but his persistence has paid off with the publication of a high impact paper in Cell in 2009 on his characterization of the human SLX4 protein as a Holliday junction resolvase subunit that binds multiple DNA repair/recombination endonucleases. Furthermore, he is co-author of a paper in press at Nature Genetics as a collaboration with a Cambridge lab, UK on the phenotypic analysis of an Slx4 knock-out mouse showing that it exhibits phenotypes similar to Fanconi anemia mutants. The other major project in the Gaillard group involves the role of phosphorylation of the Eme1 endonuclease by the Rad3 DNA checkpoint kinase in S. pombe. They have shown that this phosphorylation is required for rDNA maintenance in the absence of the Rqh1 DNA helicase. This work is being prepared for publication.

The team has continuing collaborations with two expert labs (including mass spectrometry) at the Scripps Institute, and with another lab in Cambridge (UK).

There is at present much interest and some controversy about the mechanisms of resolution of Holliday junction intermediates in genetic recombination in eukaryotes, and recently this team has made challenging high-visibility contributions to this field. They have done a particularly good job of the biochemical characterization of the enzymes involved both in human cells and in yeast.

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

Pierre-Henri Gaillard directs a small team composed of himself, a postdoctoral fellow, and a technician hired for two years with FRM funding. He indicates that two other postdoctoral fellows will be joining him in 2011, including one from Osaka University in Japan.

The funding of the team over the last four year period has come from the CNRS ATIP program, the French Association for Cancer Research, the FRM, and from a European Marie Curie International Reintegration Grant.

Gaillard is already internationally well known in his field. He was a recent speaker at 7 international conferences and he is a co-organizer, together with more senior scientists, of a large meeting on DNA repair in the Netherlands in 2011.

- Appreciation on the scientific strategy and the project

Over the next four year period, the Gaillard team plans to continue their characterization of the Eme1 endonuclease in S. pombe and of the mammalian Slx4 scaffold protein. They plan to continue their studies of why Eme1 phosphorylation is critical only in the absence of the Rqh1 helicase. They also have indications that Eme1 may be a SUMO binding protein and they would like to test this possibility and identify Sumoylated partners of Eme1. Likewise, they have identified putative SUMO and ubiquitin binding motifs in the human Slx4 sequence and they want to identify possible ubiquitylated or sumoylated partners of Slx4. Slx4 interacts with the telomeric protein Trf2, and they have preliminary results showing colocalization of Slx4 with the Rap1 telomeric protein and with ALT-PML bodies in ALT telomere-maintenance cells. They would thus like to study a possible role of Slx4 in telomere metabolism. Finally, they are engaged in structure-function analyses of this intricate scaffold protein.

The strategy of defining and characterizing relevant structure-specific endonucleases is excellent. These intriguing enzymes will most likely provide keys to understanding recombination mechanisms in molecular detail.

- Conclusion :

— Summary

Pierre-Henri Gaillard does not have a large number of research publications (13), but he has consistently published in very high impact journals at each stage of his career. The committee feels that his research interests integrate well with the other genome stability groups of this unit.

— Strengths and opportunities

The team leader has a recent high profile publication in Cell in 2009 as last author on the human Slx4 protein and he is co-author on a Nature Genetics paper in press on the characterization of an Slx4 knock-out mouse. He is thus now in good position to seek further funding and support for this project. His work on fission yeast Eme1 is also now ready for publication and should lead to another excellent publication.

— Weaknesses and threats

The team is small, has modest funding, and is working in a highly-competitive area.

— Recommendations

To take advantage of the two recent high profile publications for aggressively seeking further funding and increase the personnel on the team. The fission yeast Eme1 project is probably somewhat less competitive than the mammalian Slx4 project. On the other hand, the mammalian Slx4 project may have a higher impact and may give greater opportunities to profit from the environment of the CRCM. Given the small size of the team, some consideration should be given as to whether it might be better to focus efforts on one of the two subjects until the critical mass of the team is increased. It may also be possible to further leverage collaborative efforts to advance more quickly.

This team deserves strong support for their exciting and highly promising research studies.

Team 13 : Genome dynamics and recombination - Bertrand LLORENTE

- Staff members

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

- Appreciation on the results

Bertrand Llorente directs a recently formed team working on Genome Dynamics and Recombination. After postdoctoral work at the Pasteur Insititute, he was recruited to a CR1-CNRS position in 2007 and received an ATIP grant in 2008 to start his own team to study the mechanism of break-induced mitotic recombination and meiotic recombination events in yeast. Over the last 4 year period, he had a single publication in collaboration (second position with three authors) that was nevertheless of very high impact in Nature in 2007 demonstrating that template switching occurs during BIR in yeast.

The committee feels that the establishment of Llorente's team in Marseille is too recent to evaluate his research results. This evaluation should occur at the next evaluation of the new unit.

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

Bertrand Llorente started his team recently. He has worked with two Master's students and he had a research technician for two years. Thanks to his participation in a recently funded ANR consortium, he will be able to hire a postdoctoral fellow for two years to work on his meiotic recombination project. He has also obtained funding from the French Association for Cancer Research. He was invited to speak at two national meetings.

- Appreciation on the scientific strategy and the project

Bertrand Llorente would like to pursue his studies on the mechanism of break-induced mitotic recombination and meiotic recombination events in yeast. He has performed a genome-wide screen of the deletion collection of non-essential yeast genes to identify mutants affecting BIR. He found no mutants with BIR-specific effects other than the previously identified pol32 mutant. However, they found that the fun30 mutant shows increased levels of both BIR and gene conversion. FUN30 encodes a putative chromatin remodeller of the Swi/Snf ATPase family that has been poorly studied. Preliminary results suggest that Fun30 facilitates 5' to 3' resection of DSB ends. They would like to further verify this result and test genetic interactions with other known mutants affecting DSB resection. Chromatin and DSB repair is an expanding area of investigation, so the implication of a novel chromatin remodeller on DSB resection is important. Llorente is also testing the effect of chromosomal context on the BIR process. They have found significantly higher BIR efficiency for recombination initiated within 15 kb from the telomere end. They will test the possibility that BIR is a two step process involving a non-processive initial step followed by a more processive second step. In terms of meoitic recombination, his participation in an ANR funded consortium will allow him to hire a postdoc to determine and compare for the first time the genome wide maps of DNA DSBs and crossovers of several species in a single yeast clade.

- Conclusion :

— Summary

Bertrand Llorente's research team dates only from 2008 and he has a small team. This explains the absence of publications since his high-profile collaborative paper in Nature in 2007. His research report describes interesting unpublished results concerning his further characterization of the BIR process in yeast. The research area of this team fits well with the interests of the other teams working on genome stability.

— Strengths and opportunities

Interesting preliminary results concerning the BIR process in yeast. Participation in a funded ANR consortium that will allow the team to recruit a postdoc for his meiotic recombination project. It is unlikely that other labs are studying meiotic recombination in this fashion so there is little risk of competition.

— Weaknesses and threats

Obviously small team because of its recent creation. Given its small size, there is a risk of dispersion in studying both BIR and meiotic recombination at the same time.

— Recommendations

Given the small size of the team, it would normally seem best to initially focus on one subject ie the BIR project as it corresponds to : the continuation of the Nature study published in 2007; it may be of greater general interest and thus easier to fund ; and it is the project for which the most preliminary results have been obtained. However, the successful funding of the ANR consortium to study meiotic recombination is an offer that cannot be refused. It is nevertheless recommended to concentrate on publishing the results on the BIR project as rapidly as possible and to continue to seek funding to further reinforce this project.

Team 14 : Translational medicine and therapeutic evaluation in oncology - Anthony GONÇALVES

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	9	9
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	5	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	20	20
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)		
N7: Number of staff members with a HDR or a similar grade	8	10

- Appreciation on the results

This team was previously named clinical research division and during the last quadrennial was headed by another PU-PH who will now join team 6 in the future CRCM project. The written "past report" did not include a detailed assessment of the previous activity of this team, particularly, only publications of the previous leader were recorded. Moreover it appears from the written document that the past activity of the clinical research division overlaps or are embedded in the report activity of others CRCM teams. Therefore the committee decided to consider not be able to evaluate its past scientific activity of the team itself without a complete and specific report of the clinical research division on their past research.

As an indicator, the proposed team leader has published 4 reviews and 22 articles from 2006 to 2010. Most of them are international publications with 1 publication with an impact factor superior to 10 (1 letter in JNCI). He has published 8 articles as first or last author (among them 3 were published in journals with an impact >5 1 Oncogene, 2006, 2 Mol Cell Proteomics).

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

Several international collaborations are depicted in the project. They also developed local collaborations with different basic research teams. The future team will be composed only of MDs (PH and PU-PH) who will work 50% of their time for the team. Nothing is mentioned about the past and future recruitment of students and post-docs. In this respect, the attractiveness of the clinical team will be dependant on how their relations with the basic research teams will be set up, which are not precisely depicted. The collection of tissues and the clinical annotation associated with will be of great interest for the community of basic scientist of CRCM.

Clinicians at CRCM that are part of the present proposed team have obtained several grants as PI particularly from PHRC-INCa to set-up clinical trials (5 from 2006 to 2010). This success is clearly the result of the clinical team of research. However, attractiveness of this clinical and translational research team should be evaluated by various indicators that are not precisely provided in the report (ie. exact number of clinical trial relevant from this specific team, number of inclusions relatively to the objective, quality of the collected samples, publication related to these different funding).

Furthermore given the lack of information available, the visibility of the future team is difficult to apprehend. Of note, the group leader is expert member of several national scientific committees (INCa, CNR2C-PHRC 2007-2009, GTOH-AFSSAPS 2010) and as MCU-PH, is involved in multiple teaching tasks at the Faculté de Médecine-Université de la Méditerranée Aix-Marseille II. Only one selected oral communication of the group leader at the 2007 ASCO meeting in Chicago, US, is mentioned in the documents.

The visibility and relationship of the team with the other clinical and translational groups should be better depicted at the local, regional, national and international levels.

- Appreciation on the scientific strategy and the project

This team is composed exclusively of PUPH and MCUPH with 50% of their time dedicated to the research. Altogether the full time research personel dedicated to the project is 5.6. They rely on different biological platforms of the CRCM and Paoli Calmettes Institute to set up their research program based on innovative clinical trials. These clinical trials will be innovative through different ways (molecularly targeted, biomarker driven, innovative criteria of judgment) and focusing on four axes (malignant myeloid disorders and epigenetic therapeutics; poor prognosis breast cancer; pancreatic cancer; allogenic and non allogenic immunotherapy). These translational projects are developed in cooperation with other teams of the research centers. However the leadership of each translational research is not well depicted as well as the rules governing relations between this team and teams of basic research in terms for example of supervision of students. The existence and relevance of a policy for the allocation of resources is not clearly depicted, however a strategic board dedicated to early clinical trials has been set up and will probably put in place policy for the allocation of resources. The presented projects are relevant and interrelated with different basic scientific project of CRMC teams however as for all clinical trials they are risky in a highly competitive environment.

- Conclusion :

The team has in its hands what they need to fulfill their objectives and reach a high level of success however the absence of full time researcher is a weakness and the relation with the other researcher teams could be a source of conflict if the leadership of each translational research projects is not well depicted as it is the case in the written proposal. The existence within the CRCM of this research activity as a bona fide “team” was not obvious to the visiting committee and it remains questionable whether a translational research committee backed to platforms would not have been more appropriate. The committee considers with the written elements in its hands he is not able to really evaluate this team, we recommend to elaborate and re-deposit a completed and detailed report and project.

Team 15 : Immunity and cancer - Daniel OLIVE

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	8	6
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	7	7
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.7 of the application file)	7	
N7: Number of staff members with a HDR or a similar grade	4	4

- Appreciation on the results

The objective of the team is to identify the mechanisms by (i) which cancer cells escape immune surveillance and (ii) by which viruses induce pre-cancer lesions. These projects represent a well-balanced combination of fundamental and translational/clinical research.

The research is of high quality and benefits from a closed collaboration with the Biopathology department of the hospital (its head is a member of the team) and from extensive collaborations with several public and private hospitals and labs (including one with the Center d'Immunologie de Marseille Luminy, CIML) in Marseille. The team has developed an excellent expertise in signaling (chronic infection and tumor immunology) and in the analysis of tumor microenvironment.

The team has also created the 1st IBISA Cancer Immunomonitoring Platform.

The productivity of the team has been excellent with 58 publications since 2006, with 9 publications with IF higher than 10, as well as 7 patent applications and 10 PhD theses

The team has developed stable partnerships with clinicians from the department of hepato-gastroenterology Saint-Joseph hospital for studying innate immunity during chronic HCV infection (Marseille).
Collaborations have also been established to develop animal models to study homeostasis of the immune system with CIML in Luminy and the BIDMC in Boston, as well as for transversal projects on PI-3K pathway in tumors within CRCM (team 1) and IPC including for the use of their biobanks.

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

The team is very attractive and has strong links with international, national and local partners. There is an excellent visibility of the team leader and a strong attractiveness for PhD students. They participated to 32 conferences as invited speakers.

Several promotions and recruitment occurred in past years, including one technician, one DR2 and one PU-PH. They signed a "Contrat d'interface Inserm".

The team was successful to get funding from INCa (4 "projets libres" and one translational research), from Canceropole (restructuration axe IV), ANR RIB (1), ANRS (1) and received also funding for label IBiSA to the Cancer Immunomonitoring Platform.

The team belongs to a national network dedicated to lymphomas and has several strong partnerships with French or foreign teams in the field of cosignaling in cancer and viral infections. Four projects are being developed in collaboration with national or international teams.

- Appreciation on the scientific strategy and the project

The long-term project of D Olive's team is in continuity with his past research on cosignaling molecules used by cancer cells to inhibit immune surveillance. Previous works analyzed (1) the expression of inhibitory cosignaling molecules, the acquired deficiency of innate immunity in cancer and the potential use of cosignaling molecules as adjuvant therapies, (2) the response of plasmacytoid dendritic cells to HCV infection, (3) the role of regulatory T cell and cosignaling molecules and their ligands in the development and behavior of malignant lymphoproliferations, (4) the mechanism of lymphocyte activation and (5) the pharmacology of signaling pathways.

The organigram of the team has been modified and the project is now organized along 4 tasks:

1. In vivo expression of cosignaling receptors in the microenvironment of malignant lymphomas. This project will involve clinicians and researchers of the CRCM and a collaboration with Institute A Bonniot in Grenoble and an industry partner Beckman Coulter.

2. The study of cosignaling molecules and innate immunity in collaboration with Inserm U563 in Toulouse and Inserm U790.

3. The development of animal models to study cosignaling pathways pharmacology, in collaboration with Inserm UMR624 in Marseille and at CIML.

4. Innate immunity hijacking in chronic viral infection and cancer in collaboration with clinicians of IPC and public and private hospitals in Marseille.

These projects are of high quality and are based on the expertise and background of the team in the field. It feasibility is excellent, regarding the collaborations that have been already established.

Resources are based on grants from INCa, ANR, ANRS, PHRC, industry. The strategy of the team is to maintain a strong integration in Cancéropole PACA and Plan Cancer II.

The various projects are original and some cutting edge projects could emerge from the study of animal models generated in the lab (CD28 KI mice) or elsewhere (Dok1/2 KO mice).

- Conclusion :

  - Summary

The team "Immunity and cancer" is involved in the characterization of mechanisms by which cancer and chronic viral infection escape immune surveillance. Past research was based on a closed collaboration between researchers, pathologists and clinicians. This integrated strategy permitted the identification of negative cosignaling molecules used by cancer cells to inhibit the immune response.

One important step was the creation of a translational research structure, which had became an IBISA labeled Cancer Immunomonitoring Platform in 2008.

The new project aims at focusing on cosignaling molecules, NK and T regulatory cells as biomarkers for the prognosis and response to treatments. New animal models will help to explore the functions of costimulatory molecules implicated in homeostasis of the immune system. Several elements (size of the team ie 20-25 persons, half of them having a tenured position, financial support…) warrant the feasibility of the project.

— Strengths and opportunities

- Stable team (20-25 persons, including 12.5 permanent positions), high level of expertise in several complementary fields, critical mass.

- Efficient interactions between basic research and translational research. The IBiSA cancer immunomonitoring platform will be instrumental for some of the projects.
- National and international collaborations
- International audience in virus-induced cancer and cosignaling in immune systems in acute myeloid leukemias.
- Excellent focus on the fields of expertise of the team.

— Weaknesses and threats

The development of collaborations with pharmaceutical companies for the design of targeted therapies is recommended.

— Recommendations

Excellent project with strong inside and outside collaborations. Validation of the identified biomarkers and clinical trials should be developed in large cohorts of patients through multicentric protocols at national level to increase the power of analyses.

Team 17 : Fundamental and therapeutic chemical biology - Yves COLLETTE

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0.5	0.5
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	
N7: Number of staff members with a HDR or a similar grade	1	2

- Appreciation on the results

The team studies the pharmacology of signaling in tumor cells by mean of chemical biology approaches. Over the last period this emerging team was part of the "immunology and cancer team". Two projects have been developed over the 2006-2010 period: one devoted to the Src tyrosine kinase family, with the aim to alter Src activity by targeting protein-protein interactions via their SH3 domains (in particular the search for protein-protein interaction inhibitors), and a second project focused on epigenetic alterations in Acute Myeloïd leukemia and pharmacological targeting. The team leader has also set up a platform of preclinical trials, with the goal to develop model systems allowing to evaluate in vitro (cellular models) and/or in vivo (xenografts) the anti tumour activity of drugs. He contributed 6 papers as last author (J Med Chem, Mol Cell Biol, Plos One, Biotechniques, PNAS, J Biol Chem) and co-authored 6 other papers (among them J Med Chem, Plos One). He also contributed to two patents.

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

The team is currently composed of the team leader, one CR1 CNRS who is expected to join the team early in 2011, two post-docs, one PhD student, one M2 and a part time technician. Collaborations are developed within the center and abroad. The platform is also opened to either collaborative work or on a service basis. Funding has been obtained from ARC (subvention fixe 2010) and ANRS (2009-2010). The team also benefits from a "contrat d'interface Inserm-IPC" for translational research developments with a team at IPC.

- Appreciation on the scientific strategy and the project

Over the next four year period, the team plans to continue the characterization and development of epigenetic drug inhibitors such as DNA demethylating agents and histone deacetylase inhibitors. A drug proteomic approach using immobilized compounds onto affinity columns will be developed for Vorinostat/SAHA and novel derivatives designed and synthesized by the team. Improving the specificity of such deacetylase inhibitors is also envisioned. The team will also target the SUV39H1 histone methyl transferase in AML. The association with a chemist strengthens the strategy of the team for their drug proteomic and design approaches (still requires strong collaborations for in silico design, screening…). New avenues of research are also envisioned with the arrival of strong teams from UPR3081.

- Conclusion :

— Summary

The team brings a multidisciplinary expertise to the center, with the development of chemical biology approaches for drug proteomics and drug design. It has consistently published in good journals.

— Strengths and opportunities

The team has extended its expertise with the arrival of a chemist, which reinforces the potential to boost drug proteomic and design. The proposed evolution of the Center should also increase the number of projects in which the team can bring a significant input. This team has an important task to fulfill in the new Center, in bridging fundamental and more clinically oriented researches with chemical biology approaches.

— Weaknesses and threats

The team has still to rely on external expertise for the requested input in structure based/in silico drug design and discovery. Also, all the infrastructures for chemical synthesis are in another center and thus access may not be guaranteed. The team is small and has to manage both research projects and the platform of clinical trials. The frontier between proprietary research and high tech service platform may prove difficult to manage.

— Recommendations

The team would benefit from the close relationship that could emerge with new coming teams from the CNRS (formerly UPR3081). This relationship should strengthen its strategy towards cancer target and drug discovery at a more fundamental level by adding a strong molecular background to the projects.

Team 18 : Antibody therapeutics and immunotargeting - Daniel BATY

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	3	
N6: Number of Ph.D. students (Form 2.7 of the application file)	5	
N7: Number of staff members with a HDR or a similar grade	2	3

- Appreciation on the results

The team previously belonged to the Inserm U624 "Stress cellulaire". During the past 4 years, members of the team have focused their activities on therapeutic antibodies, and in particular on bispecific antibodies, aiming to target immune effector cells to tumor cells. Although this objective is not highly original, the team used a novel approach, the nanobodies, based on high affinity single variable domains of llama heavy chains antibodies. Using this strategy, they developed a bispecific antibody to redirect NK or T cells to the CEA antigen. This team also aims, in collaboration with team 10, at developing intrabodies to target intranuclear telomeric protein and to set up nanobody chips for cancer diagnosis and identification of new therapeutic targets.

One important achievement of the team is the development of a nanobody platform (unique in France), which is supported by a European FP7 framework project and by a national program (Fonds Unique Interministériel) in collaboration with CisBio. The development of this platform will open opportunities to the CRCM to develop antibodies with diagnostic or therapeutic potential.

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

The numbers of original publications, as well as the impact factors of the publications, are quite modest considering the size of the team and the number of permanent staff members.

The report lacks critical information on scientific communications, thesis and other outputs.

The team has participated to several international or national meetings but no information was available in the written report.

This team comprised three full-time researchers (including one CR1 recruited in 2005), five PhD students and three non-permanent research engineers.

From 2005 to 2010, the team successful applied to 6 national grants (ANR/2INCa/ANRS/Inserm/OSEO) and one FP7 European grants.

Information was however lacking on the role of the team in these various projects (PI, partners…) as well on the budgets allocated.
This team collaborates with several teams, including teams in CRCM and Nice (UMR S998), and as already opened the Nanobody platform to the academic teams of CRCM.
Two patents were granted and two are pending.

Partnership has been established with CisBio International and Sanofi for developing nanobodies to G-coupled receptors, receptor tyrosine kinases and ion channels.

- Appreciation on the scientific strategy and the project

The current project first aims to develop therapeutic antibodies in direct continuation of previous work. The team will continue its work on redirecting NK or T cells, using the CEA antigen as a tumor target. They will validate this strategy in a mouse model of pancreatic cancer or in humanized mice.

The second part of the project focuses on the development of intrabodies targeting telosome and TP53INP1.

Finally, one important objective of the team is to increase the valorisation of the platform which in 2012 will be opened to all academic team. An application for the IBiSA label will be shortly filed.

Overall, the project could lead to the development of new tools to interfere with protein-protein or protein-DNA interactions as well as new therapeutic strategies for personalized medicine by selecting nanobodies against tumor markers.

There is no doubt that a team focusing on therapeutic antibodies is fully justified in Center of Cancerology. The projects are interesting, with some being relatively classic and other more innovative. It will be important to develop a precise strategy to move toward clinical trials.

Resources are collected for starting the platform. However, information are lacking on the resources available for the next few years.

- Conclusion :

— Summary

This team has used its specific expertise in the field of nanobodies to set up a platform which aims at developing nanobodies to tumor markers.

— Strengths and opportunities

- Three full-time researchers with good expertise in the field.
- The Nanobody platform is an interesting initiative at the national level

— Weaknesses and threats

- Basic research may suffer from the development of a high throughput platform.
- The team lacks appropriate in vivo models and well-defined strategies for achieving pre-clinical proofs of concepts. A better selection of projects would be required for allocating resources to the most promising nanobodies.

— Recommendations

A scientific council could be necessary to select the projects, which will be developed by the Platform.

The team has also to better define its strategy and to focus on a more limited number of objectives to increase it competitiveness.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
CRCM - CENTRE DE RECHERCHE EN CANCÉROLOGIE DE MARSEILLE	**A+**	**A**	**A+**	**A**	**A**
ADHESION MOLECULES IN HOST-TUMOUR INTERACTION [BORG-AURRAND-LIONS]	Non noté	B	Non noté	A	A
TUMOUR CELL MOTILITY [BORG-BADACHE]	A	A	Non noté	A	A
ANTIBODY THERAPEUTICS AND IMMUNOTARGETING [BORG-BATI]	A	B	Non noté	B	B
MOLECULAR ONCOLOGY [BORG-BIRNBAUM]	A+	A+	Non noté	A	A+
CELL POLARITY, CELL SIGNALLING AND CANCER [BORG-BORG]	A+	A	Non noté	A+	A+
FUNDAMENTAL AND THERAPEUTIC CHEMICAL BIOLOGY [BORG-COLLETTE]	A	B	Non noté	B	B
SIGNALLING, HAEMATOPOIESIS AND MECHANISMS OF ONCOGENESIS [BORG-DUBREUIL]	A	A	Non noté	A	A
EPIGENETIC CONTROL OF NORMAL AND PATHOLOGICAL HAEMATOPOIESIS [BORG-DUPREZ]	A	B	Non noté	A	A
TOLERANCE TO DNA LESIONS [BORG-FUCHS]	A+	A+	Non noté	A+	A+
CONTROL OF STRUCTURE SPECIFIC ENDONUCLEASE AND GENOME STABILITY [BORG-GAILLARD]	A+	A	Non noté	A+	A+
TOLERANCE, SENESCENCE AND DNA DAMAGE [BORG-GELI]	A+	A+	Non noté	A+	A+
TRANSLATIONAL MEDICINE AND THERAPEUTIC EVALUATION IN ONCOLOGY [BORG-GONCALVES]	Non noté	Non noté	Non noté	Non noté	Non noté
CELL STRESS [BORG-IOVANNA]	A+	A	Non noté	A	A
GENOME DYNAMICS AND RECOMBINATION [BORG-LLORENTE]	Non noté	B	Non noté	B	B
MECHANISMS OF DNA DOUBLE STRAND BREAK REPAIR SYSTEM: HOMOLOGOUS RECOMBINATION AND NHEJ [BORG-MODESTI]	Non noté	B	Non noté	A+	A
IMMUNITY AND CANCER [BORG-OLIVE]	A+	A	Non noté	A+	A+
PDZ SCAFFOLD PROTEINS AND PHOSPHOINOSITIDES IN CELL SIGNALLING AND ONCOGENESIS [BORG-ZIMMERMANN]	A	A	Non noté	A	A

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

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

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

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

- **SVE1 Biologie, santé**
  - **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
  - **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
  - **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
  - **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
  - **SVE1_LS5 Neurosciences**
  - **SVE1_LS6 Immunologie, Infectiologie**
  - **SVE1_LS7 Recherche clinique, Santé publique**
- **SVE2 Ecologie, environnement**
  - **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
  - **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
  - **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

UNIVERSITÉ DE LA MÉDITERRANÉE
AIX-MARSEILLE II

Objet : Réponse au rapport d'évaluation - **S2UR120001656 - CRCM - Centre de Recherche en cancérologie de Marseille - 0131843H** - de l'unité CRCM - Centre de Recherche en cancérologie de Marseille

Observations d'Aix-Marseille Université

Le Comité a reconnu que la recherche clinique est l'un des atouts et une des réussites majeures du Centre, mais il est resté réservé quant à la création d'une équipe de Recherche Clinique qui pourrait cloisonner les échanges et collaborations avec les biologistes. La recommandation du Comité sera suivie en ne maintenant pas cette proposition. Les projets présentés au sein de cette équipe seront réaffectés aux équipes de biologistes avec lesquelles collaborent les cliniciens (Equipes D. Birnbaum, D. Olive, J. Iovanna, J.-P. Borg et Y. Collette). Le Comité recommande cependant la création de deux Départements « Oncogenèse et dissémination métastatique » et « Innovations thérapeutiques » permettant une animation scientifique optimale et une meilleure synergie entre les équipes, avec le lancement de projets collaboratifs pilotes. Ces projets ont déjà commencé au cours de la période 2010-2011 et plusieurs réunions entre équipes des 3 unités ont eu lieu en 2010 et 2011, avec un séminaire général des 3 unités en 2010. Depuis 2010, la Direction de l'Institut Paoli-Calmettes a créé une nouvelle dynamique dans le secteur recherche en créant des « teams » thématisés sur des axes priorisés (sein, hématologie, digestif) rassemblant cliniciens et biologistes de façon régulière et organisée (réunion mensuelle, leader : JF Saunière, MDPhD, IPC). Ces réunions permettent aux différents acteurs (IPC, CRCM, U 624, IGC) de présenter leurs travaux amont et aval, d'échanger de nouvelles idées, d'élaborer de nouveaux programmes collaboratifs et de concourir à des financements communs sur des appels compétitifs. Cette stratégie a déjà porté ses fruits en 2011. Citons parmi les projets pilotes déjà lancés, un projet « pancréas » porté par Juan Iovanna, réunissant les cliniciens de l'Institut Paoli-Calmettes et l'équipe de Daniel Birnbaum (PACAomics, présélectionné à l'appel d'offre INCa translationnel 2011), un projet pancréas collaboratif entre l'équipe de Juan Iovanna et Patrice Dubreuil (PLoS One 2010), et un projet « épigénome » associant les équipes de Yves Collette et de Vincent Géli (présélectionné à l'appel d'offre INCa libre et programme ARC 2011).Sur le plan organisationnel, comme suggéré par le Comité dans ses recommandations, les espaces alloués à chaque équipe, la gouvernance et le mode de fonctionnement du Centre seront clairement établis par écrit au cours de l'année 2011.

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Le Comité a mentionné par erreur un Comité Exécutif composé uniquement de 2 personnes. Comme indiqué en page 21 du projet CRCM, ce Comité comprendra en fait le Directeur et les 2 sous-Directeurs, le Directeur Général de l'IPC, Françoise Birg, 5 chefs d'équipe seniors et le responsable du Centre de Ressources Biologiques de l'IPC.

Equipe Patrice Dubreuil

- Comme mentionné pendant l'audition, l'équipe a obtenu pour la troisième fois son Label Ligue National Contre le Cancer (2011-2013) et un financement de la FRM en physiopathologie.
- *"L'équipe ne propose pas un plan de validation des cibles potentielles qui émergeront de son crible sur échantillons humains":* Comme précédemment fait pour les kinases Fes et Fer, des lignées cellulaires et, quand il sera possible, des échantillons humains, seront utilisés avec des inhibiteurs ou des siRNA pour la validation des cibles thérapeutiques. L'activité des kinases et la recherche de mutations seront déterminés dans les échantillons humains adéquats ».
- *"Quelles sont les lignées cellulaires dans lesquelles les mutations Fes/Fer ont été trouvées? Pourquoi l'équipe choisit-elle les tumeurs ...(effacé car confidentiel) ?* Les mutations Fes/Fer ont été trouvées dans ces lignées cellulaires et tumeurs primaires citées expliquant pourquoi elles ont été mentionnées pour être utilisées dans le projet.

Equipe Pierre-Henri Gaillard

Cette équipe a plusieurs collaborations nationales et internationales avec des experts du Scripps Institute, de l'ICGEB à Trieste (spectrométrie de masse), de l'Université d'Oslo (cristallographie rayons X), de Stony Brooks University et de l'Université de Nice. Cette équipe comprend le chef d'équipe, 2 post-doctorants, un technicien CNRS, et un ingénieur FRM en CDD. Un postdoctorant venant de l'Université d'Osaka rejoindra l'équipe en 2011. PH Gaillard a été co-organisateur et orateur d'un meeting national « DNA repair, recombination and replication" qui s'est tenu en France in 2011, en plus des conférences citées dans le rapport.

Equipe Yves Collette

Concernant l'international et les financements, l'équipe a été invitée à rejoindre un programme européen EC COST « TD-09-05 Epigenetics : bench to bedside » en 2011. Les collaborations internationales impliquent: Italie = C. Sette, L. Altuci; Belgique = F. Dequiedt, C. Van Lint; USA = S. Arold, T. Smithgall.
En plus des financements mentionnés (ARC fixe 2010 and ANRS 2009-10), l'équipe est présélectionnée pour un programme INCa Libre 2011 et un Programme ARC 2011, et avec la plateforme préclinique TrGET, bénéficie d'un financement industriel (Servier).

Equipe Daniel Baty

Le Comité a noté que le nombre de publications est relativement modeste au regard de la taille de l'équipe, en se referrant à une équipe composée de 3 chercheurs statutaires, 5 étudiants en Thèse et 5 ingénieurs non statutaires. Concernant les chercheurs statutaires, Daniel Baty était le seul jusqu'en 2006 quand Patrick Chames a été recruté CR1. Le 3ème chercheur, Brigitte Kerfelec, CR1, a rejoint l'équipe seulement très récemment (2009) et

travaillait auparavant dans un champ d'expertise très différent. De plus, 2 étudiants en Thèse n'ont rejoint que très récemment l'équipe (Octobre 2010) grâce à de nombreux financements obtenus par l'équipe, et ne peuvent donc pas être comptabilisés dans la production de l'équipe.
Concernant le manque d'informations sur la participation aux congrès internationaux et la liste de publications dans le rapport papier, un document écrit contenant toutes ces informations a été envoyé avant la visite du comité et donné au comité pendant l'évaluation sur site pour compenser cette regrettable erreur.
Concernant les financements, ces données ont été fusionnées avec celles de l'U624 U 624 Stress Cellulaire dans le rapport papier (doc BILANS), rendant peu lisible cette information aux yeux du comité. La plateforme est actuellement financée par 2 grands programmes (OSEO and FP7) jusqu'en 2015. Le développement d'animaux modèles a été retardé (2 ans) du fait de l'ouverture retardée de l'animalerie de l'U624 Inserm. La stratégie d'avancer nos projets les plus avancés vers des essais cliniques a été précisée depuis la visite du comité puisque nous comptons, avec Inserm-Transfert, collaborer avec deux grandes sociétés pharmaceutiques (Servier et MedImmune).
Plusieurs projets ont débuté lorsque l'équipe travaillait dans l'unité CNRS précédente et seront bientôt terminés, ce qui permettra à l'équipe d'être plus compétitive sur ces projets phares et de focaliser sur des projets prioritaires.

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

Le Président
de l'Université de la Méditerranée

Yvon BERLAND

Le Vice-président du Conseil Scientifique
de l'Université de la Méditerranée

Pierre CHIAPPETTA

Centre de Recherche en Cancérologie de Marseille
Unité Mixte de Recherche (UMR 891)

Madame la Présidente du Comité d'évaluation de l'AERES,

Je commencerai par vous remercier, ainsi que les membres du comité AERES et le Délégué AERES, pour la qualité de l'expertise que vous avez menée au sein de notre Unité de Recherche les 26-28 janvier 2011 en présence de nos institutions.

A la lecture du rapport qui nous est parvenu, nous sommes heureux de constater que le Comité a apprécié l'effort de structuration fait par les 3 structures actuelles, le CRCM (UMR 891 Inserm), l'IGC (UPR 3081 CNRS) et l'UMR 624 Inserm, pour proposer la création d'un Centre de Recherche en Cancérologie couvrant des thématiques prioritaires - mécanismes de l'oncogenèse, relations hôte-tumeur, instabilité du génome et réparation de l'ADN -, basé sur un projet scientifique cohérent et attractif, rassemblant des équipes performantes dans leurs domaines respectifs. Ce projet ambitieux aborde ces thématiques de recherche dans une démarche très transversale, de la biologie fondamentale à la recherche translationnelle et clinique, en parfaite cohérence avec le potentiel scientifique et médical des équipes Inserm, CNRS, et de l'Institut Paoli-Calmettes. Ce projet bénéficie de l'appui total de l'Université de la Méditerranée. Comme il est souligné dans le rapport, ce projet s'adosse à une recherche de haute qualité démontrée par les résultats obtenus par les équipes lors du quadriennal 2008-2011, à des plateformes très bien organisées, à une forte volonté de la communauté médicale et scientifique de créer une vraie masse critique de recherche sur le cancer au sein de l'Institut Paoli-Calmettes, à l'opportunité donnée à de jeunes équipes (Avenir Inserm, ATIP CNRS, EMBO YIP) de créer leur équipe, et à une gouvernance réaliste. Nous sommes heureux de constater que le Comité est très favorable à notre stratégie visant à faire des thématiques « instabilité du génome et dommages de l'ADN » et « cancer du pancréas », deux thématiques prioritaires et intégrées du CRCM, avec un fort appui de l'Institut Paoli-Calmettes. Nous suivrons la recommandation du Comité en implémentant le Conseil Scientifique du CRCM de nouveaux membres spécialisés dans ces champs d'investigation.

Le Comité a également émis d'autres recommandations et interrogations auxquelles je souhaite répondre spécifiquement.

Le Comité a reconnu que la recherche clinique est l'un des atouts et une des réussites majeures du Centre de recherche, mais il est resté réservé quant à la création d'une équipe de Recherche Clinique qui pourrait cloisonner les échanges et collaborations avec les biologistes. Nous suivrons la recommandation du Comité en ne maintenant pas cette proposition. Les projets présentés au sein de cette équipe seront réaffectés aux équipes de biologistes avec lesquelles collaborent les cliniciens (Equipes D. Birnbaum, D. Olive, J. Iovanna, J.-P. Borg et Y. Collette). Le Comité recommande cependant la création de deux Départements « Oncogenèse et dissémination métastatique » et « Innovations thérapeutiques » permettant une animation scientifique optimale et une meilleure

synergie entre les équipes, avec le lancement de projets collaboratifs pilotes. Ces projets ont déjà commencé au cours de la période 2010-2011 et plusieurs réunions entre équipes des 3 unités ont eu lieu en 2010 et 2011, avec une retraite générale des 3 unités en 2010. J'ajouterai, que depuis 2010, la Direction de l'Institut Paoli-Calmettes a créé une nouvelle dynamique dans le secteur recherche en créant des « teams » thématisés sur des axes priorisés (sein, hématologie, digestif) rassemblant cliniciens et biologistes de façon régulière et organisée (réunion mensuelle, leader : JF Saunière, MD-PhD, IPC). Ces réunions permettent aux différents acteurs (IPC, CRCM, U 624, IGC) de présenter leurs travaux amont et aval, d'échanger de nouvelles idées, d'élaborer de nouveaux programmes collaboratifs et de concourir à des financements communs sur des appels compétitifs. Cette stratégie a déjà porté ses fruits en 2011. Citons parmi les projets pilotes déjà lancés, un projet « pancréas » porté par Juan Iovanna, réunissant les cliniciens de l'Institut Paoli-Calmettes et l'équipe de Daniel Birnbaum (PACAomics, présélectionné à l'appel d'offre INCa translationnel 2011), un projet pancréas collaboratif entre l'équipe de Juan Iovanna et Patrice Dubreuil (PLoS One 2010), et un projet « épigénome » associant les équipes de Yves Collette et de Vincent Géli (présélectionné à l'appel d'offre INCa libre et programme ARC 2011).

Sur le plan organisationnel, comme suggéré par le Comité dans ses recommandations, les espaces alloués à chaque équipe, la gouvernance et le mode de fonctionnement du Centre de Recherche seront clairement établis par écrit au cours de l'année 2011.

Le Comité a mentionné par erreur un Comité Exécutif composé uniquement de 2 personnes. Comme indiqué en page 21 du projet CRCM, ce Comité comprendra en fait le Directeur et les 2 sous-Directeurs, le Directeur Général de l'IPC, Françoise Birg, 5 chefs d'équipe seniors et le responsable du Centre de Ressources Biologiques de l'IPC.

Je souhaite également vous transmettre les réponses spécifiques de certains chefs d'équipe aux questionnements du Comité :

Equipe Patrice Dubreuil

- *"Applications in 2011: LNCC (label), FRM ??":* As mentioned during audition, we have obtained for the third time a renewal of the Label LNCC for the period 2011-2013 and obtained a FRM physiopathology grant.
- *"The applicant team does not propose a validation plan for potential targets that will emerge from this screen in human samples":* As previously done with Fes and Fer kinases, cell lines and when possible primary samples will be challenged with inhibitors and RNAi to validate novel therapeutic targets. The activity of the kinases and the search for mutations will be determined in the corresponding malignant tissues.
- *"Which are the tumor cell lines in which Fes/Fer mutations have been found? Why does the applicant chose …….<u>erased to keep confidential</u> …..tumours. ?* The Fes/Fer mutations were

found in cell lines and primary tumour of the proposed tumours. For this reason, these malignancies were chosen for follow-up studies.

Equipe Pierre-Henri Gaillard

Cette équipe veut mentionner qu'elle a plusieurs collaborations nationales et internationales avec des experts du Scripps Institute, de l'ICGEB à Trieste (spectrométrie de masse), de Oslo University (X-ray crystallography), de Stony Brooks University et de l'Université de Nice. Cette équipe comprend le chef d'équipe, 2 post-doctorants, un technicien CNRS, et un ingénieur FRM en CDD. Un post-doctorant venant de Osaka University rejoindra l'équipe en 2011. PH Gaillard a été orateur d'un meeting national « DNA repair, recombination and replication" qui s'est tenu en France in 2011, en plus des conférences citées dans le rapport.

Equipe Yves Collette

"If appropriate for the visiting committee, we would like to mention the following to be considered into the section « Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners ». The team was recently invited to join the EC COST « TD-09-05 Epigenetics : bench to bedside » in 2011. Collaborations abroad involve: Italy = C. Sette, L. Altuci; Belgium = F. Dequiedt, C. Van Lint; USA = S. Arold, T. Smithgall. In addition to the mentioned funding (ARC fixe 2010 and ANRS 2009-10), the team is pre-selected for the current application call by INCa Libre 2011 and Programme ARC 2011, and together with the TrGET platform, it benefits from a funding by the industry (Servier)".

Equipe Daniel Baty

"The committee noted that the number of publications is quite modest considering the size of the team, referring to a team composed of three permanent members, five PhD students and five non-permanent research engineers. Indeed, concerning permanent members, Daniel Baty was the only permanent member until 2006 when Patrick Chames was recruited as CR1. The third member, Brigitte Kerfelec, CR1, only joined the team very recently (2009) and was working on a very different field. Furthermore, 2 new PhD students have very recently joined (Oct. 2010) the team thanks to several successful grant applications, and thus cannot be taken in account concerning the outcome of the team.

We apologize concerning the lack of information about attendance to international meetings and publication lists in the written report resulting from an internal miscommunication. A written document containing all the information had been sent on due date prior to the evaluation day to correct this mistake. Unfortunately, this document was not distributed to the committee. We would like to mention that this information had been printed in emergency and given to the committee during the evaluation day to compensate for this mistake. Concerning the financial resource, this information has been given but merged with the data of U 624 (doc BILANS), which made it difficult

for the committee to interpret. The platform is actually funded by two large projects (OSEO and FP7) until 2015. The developments of animal models have been significantly delayed (2 years) by the opening of the new animal house initially scheduled for our arrival at U624 Inserm. Strategies to move the most advanced projects toward clinical trials have been defined since we are planning, together with Inserm-Transfert, to collaborate with two large biopharmaceutical companies (Servier and MedImmune). Finally we agree that we will benefit from focusing on some lead projects. Several projects started while we were working for CNRS and will end up soon, which will allow us to be more competitive on our core projects."

Equipe Michel Aurrand-Lions

*"*We thank the committee for the in depth evaluation conducted at CRCM. In one aspect, the experts felt that the visibility through high impact factor journal publications and international congress participation should be improved. This is most likely due to heterogeneity among the teams of CRCM and we think that the junior teams are a driving force to that. For example, all members of my team contributed to the CRCM visibility through participation to international congress as invited speakers or selected oral presentations (EMBO and International Immunology meeting, 2010), although the team has been solely created in 2007.*"*

Je vous prie, Madame la Présidente de la Commission AERES, d'agréer mes meilleures salutations.

Jean-Paul Borg