IRCM - Institut de recherche en cancérologie de Montpellier

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Institut de Recherche en Cancérologie de Montpellier

IRCM

Under the supervision of the following institutions and research bodies:

Université de Montpellier 1 - UM1

Institut National de la Santé et de la Recherche Médicale - INSERM

December 2013

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

Department for the evaluation of research units

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

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

On behalf of the expert committee,

- Mr. François VALLETTE , chair of the committee

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

Evaluation report

This report is the result of the evaluation by the experts committee,the composition of which is specified below.

The assessment contained herein are the expression of independent and collegial deliberation of the committee.

Unit name:	Institut de Recherche en Cancérologie de Montpellier
Unit acronym:	IRCM
Label requested:	UMR_S
Name of Director (2013-2014):	Mr André PÈLEGRIN
Name of Project Leader (2015-2019):	Mr Claude SARDET

Expert committee members

Chair:	Mr François VALLETTE, University of Nantes
Experts:	Mr Alex DUVAL, Pierre and Marie Curie University, Paris
	Mr Jean-Jacques FOURNIE, Paul Sabatier University, Toulouse (représentive of CSS INSERM)
	Mr François GHIRINGELLI, University of Bourgogne, Dijon
	Ms Giuseppa GIGLIA-MARI, Paul Sabatier University, Toulouse
	Mr Udo JESCHKE, Ludwig-Maximilians Universität München, Germany
	Mr Antonio MOSCHETTA, University of Bari, Italie
	Ms Agnès NOËL, University of Liège, Belgique
	Ms Claire RODRIGUEZ-LAFRASSE, University Lyon 1
	Mr Didier TROUCHE, Paul Sabatier University, Toulouse

Scientific delegate representing the AERES:

Mr Jean ROSENBAUM

Representatives of the unit's supervising institutions and bodies:

Mr Philippe AUGE, University Montpellier 1

Mr Michel DESARMENIEN (Director of Doctoral School n°168)

Ms Marie-Josèphe LEROY-ZAMIA, INSERM

1 • Introduction

History and geographical location of the unit

The Institut de Recherche en Cancérologie de Montpellier (IRCM), U896 INSERM, has been officially established in 2007 as an Inserm Center through the partnership of the Université de Montpellier 1, the Cancer Hospital (former CRLC Val d'Aurelle recently renamed ICM for "Institut Cancer Montpellier") and Inserm. The purpose of IRCM, since its creation, is to increase to the continuum between fundamental, translational and clinical researches in oncology (mostly in solid tumors). IRCM is located in three buildings located on the ICM / Cancer Hospital campus, with the latest building available only since September 2013, with the support of a joint funding from région Languedoc Roussillon, Université de Montpellier 1 and INSERM. To this increase in surface corresponds an increase in the number of scientists and teams affiliated to the institute. The IRCM has established several links with other local research institutes through national programs especially the INCa/SIRIC (the French type of Comprehensive Cancer Center).

Management team

The direction of IRCM (shared by the director and the deputy director) is assisted by a "Secrétaire Général" and a Lab Manager in charge of the administration and budget of the Institute. The current director is Mr André PÈLEGRIN with Mr Charles THEILLET as deputy director. For the next 5 years the proposed direction is Mr Claude SARDET as director and Mr Pierre MARTINEAU as deputy director. A consulting board of team leaders has also been constituted to represent the IRCM personnel and to help the director in the strategic decisions and politics.

AERES nomenclature

SVE1_LS4, SVE1_LS2, SVE1_LS3

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	13	17
N2: Permanent researchers from Institutions and similar positions	40	42
N3: Other permanent staff (without research duties)	27	26
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	14	18
N6: Other contractual staff (without research duties)	9	7
TOTAL N1 to N6	**103**	**110**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	22	
Theses defended	52	
Postdoctoral students having spent at least 12 months in the unit*	23	
Number of Research Supervisor Qualifications (HDR) taken	10	
Qualified research supervisors (with an HDR) or similar positions	43	43

2 • Assessment of the unit

Strengths and opportunities related to the context

This institute gathers many outstanding teams in the field of oncology and basic cancer biology. This is attested by several publications in high profile journals (such as Nature, Nat Med, Autophagy...). Several team leaders have a very strong national and international reputation, are actively involved in several national and international networks and regularly invited to write comments and reviews in prestigious journals. Most of IRCM teams have established strong and fruitful links with clinical departments, which has allowed significant diagnostic and therapeutic breakthroughs. The participation of IRCM in the SIRIC could help attract young researchers and improve synergies with clinicians and with other Institutes in Montpellier.

The IRCM is in close vicinity with Cancer Hospital, which should improve the overall visibility and attractiveness of the participating teams and the Institute as a whole. The proposed organization should foster new synergies and facilitate emergence of new teams. The proposed project appears to be adequate in order to create an internationally recognized Institute leader in its field.

Weaknesses and threats related to the context

The participating teams are currently scattered all over the campus in different buildings, even if these buildings are very close, the future direction should find ways to gather often the personnel of the IRCM to facilitate collaborations between the teams and the success of joint actions. This is particularly acute as an important proportion of the teams consists of newly formed ones and they will probably need some assistance and persuasion to create a community with extensive and creative exchanges.

Recommendations

The committee felt that the proposed project was very well thought and that obstacles and caveats were already anticipated. However, although it seems logical that all projects have a translational aspect, basic research should be maintained. A clear policy to coordinate team expansion and go/no go criteria to meet should be defined as soon as possible for all teams, especially the most recent ones.

In addition, the direction should enhance interactions among PhDs and post-doctoral fellows from different teams of the IRCM. The life of the unit needs to be enhanced and rules, especially those scheduled and described in the internal rules, must be respected if not re-enforced and in some cases created. The staff should be participating more in the life of the unit and information regarding IRCM policy better dispatched among the personnels.

The new direction should implement programmes for common policies and actions regarding:

-PhD programs,

-Internal seminars among the teams,

-Administrative support (e.g. informatics...) especially for the new teams,

-Attendance and presentation at meetings,

-Organization of retreats involving the whole institute.

The relationships with other local institutes and in particularly through the SIRIC program should be better defined.

3 • Detailed assessments

Assessment of scientific quality and outputs

The IRCM has been instrumental in the success of the Montpellier community in recent french competitive calls evaluated by international juries such as several LaBex (laboratories of excellence) like EpigenMed and MabImprove.

IRCM is a major actor in the Montpellier SIRIC (Integrated site in cancer research) which is headed by Professor Marc YCHOU (IRCM Team15) and organised along 4 main programs, two of them with WP leaders from IRCM. IRCM is a key player of the Cancer Research axis of the Pôle-Rabelais (WP representative, Mr André PÈLEGRIN IRCM), an initiative of the université de Montpellier to structure Research along main programs. It is also strongly involved in the animation of the Cancéropole Grand Sud-Ouest. IRCM is involved in other national (Carte d'identité des tumeurs/ ligue contre le Cancer) and many international programmes including numerous European Union funded projects. The IRCM has hired so far very few foreign post docs. However, for the future project the IRCM has been able to attract an impressive numbers of good young researchers from different fields and to assemble them into a strong and coherent project.

The scientific production of the IRCM is extremely variable with publications in journals ranging from average to excellent (e.g. from BBRC to Nature). The teams have very good to outstanding publication records in journals such Nature, Cell, Cancer Cell...,however mainly through collaborations and previous laboratories.

Clearly, over the past five years the policy of IRCM has considerably increased its visibility and reputation as a first class cancer research unit in France and in Europe. The recent success of its international call for recruitment of young team leaders is a sign of the great success of this policy and its international attractiveness. However, an effort is necessary for the participation in world-class scientific networks, especially trans-atlantic ones.

Thus, the IRCM is a major actor in cancer research at the regional, national and international levels with an excellent academic reputation especially in the translational aspects of cancer research, which is evidenced by its capacity to attract new scientists and teams. IRCM has developed strong links between the ICM and research teams which will be maintained and amplified in the new project.

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

The IRCM is involved in many scientific networks at local, national and international levels and members of the insitute have been participating in the organisation of local and national meetings. Members of the IRCM have an interactions with European and French charities organisation and an impressive list of patents (more than 34 including 7 licensed in the past 5 years) and industrial collaborations. This trend will certainly be increased by the new teams in the future.

Assessment of the unit's organisation and life

The IRCM current staff includes 11 teams and 129 people, including 55 permanent staff scientists, 41 technicians, 14 post-doctoral researchers and 19 PhD students. The IRCM is divided into 3 themes:

-Nuclear Receptors and hormone-dependent cancers,

-Cancers profiling,

-Therapeutic antibodies.

In the new proposal (2015-2019), IRCM will be organized in 15 teams that should increase the size of the institute up to 150/160 people. In the project, IRCM will be divided into 2 main axis:

-Therapeutic Antibodies to target Cancer: innovation, design and biological response,

-Phenotypic, genetic and epigenetic plasticity of solid tumors: from discoveries to personalized medicine.

The current director is Mr André PÈLEGRIN with Mr Charles THEILLET as deputy director, in the next 5 years Mr Claude SARDET is the proposed director and Mr Pierre MARTINEAU the deputy director. The direction of IRCM is shared by

a Director and a Deputy Director assisted by a "Secrétaire Général" and a Lab Manager in charge of the administration and budget of the Institute. A consulting board of team leaders has also been constituted to represent the IRCM personnel and to help the director in the stragtegic decisions and politics. A written internal policy defines the common rules for IRCM personnel as well as policies and organizations of support services/ technological facilities/platforms.

An external scientific advisory board (SAB) composed by high profile international cancer specialists is also part of the decision making policy of IRCM and the last visit of the SAB (march 2013) has been instrumental in the shaping of the new project. The SAB has so far been an important asset for the organisation of the IRCM and should be maintained. The proposed organisation is classical and seems to be adapted to the institute. Nonetheless, due to the important number of new teams with junior leaders, a special organisation for the "coaching" and for the help in "decision making" should be organized between the SAB, the directors and the junior team leaders. Special helps for admistrative task should also be devoted for these teams.

Assessment of the unit's involvement in training through research

IRCM personnel has been implicated in teaching in different local universities and at different levels (undergraduate and graduate degrees) both in science and medicine. Members of IRCM have created an international Master in cancer biology which started in September 2013. IRCM has trained a significant number of PhD students in the past 5 years. Discussion with the director of the Doctoral studies (Ecole Doctorale Sciences Chimiques et Biologiques pour la Santé (CBS2)) confirmed that IRCM fully respected the rules. 45 members of the current proposal have received from French Universities the authorization to supervise PhD students through the "HDR" diploma. In 2008-2013, 26 PhD thesis were defended by IRCM students and 21 are still in process. A guideline for PhD students with strong recommendations is part of the "Règlement Intérieur "of the Institute. As an example, PhD students are encouraged to present their work in at least, one international conference. 43 post doctoral fellows have been working during the same period funded by various sources from Industrial grants, Charities fellowships, European agencies… More than a third of the PhD students and post docs are foreigners, a good indicator of the international visibility and attractiveness of the IRCM.

Members of the IRCM are lecturing at the undergraduate level as part of their professional duties. Numerous internships were provided by IRCM for master students for Montpellier and foreign universities.

Assessment of the strategy and the five-year plan

The strategy in the five-year plan is supported by the new director Mr Claude SARDET and the proposition of the creation of new teams headed by young researchers. "New teams" represent 9 out of the 15 teams proposed in the next five-year plan. This means a profound re-organization of IRCM. Each team has a strong expertise in its field and has proved, at least for most of them, a capacity to secure important financial supports. The project is strong and coherent and synergies between research projects appear, in most cases, obvious.

Changes and policies have been evaluated by the SAB which will be gathered every two years for implementing and strengthening IRCM policies. Considering the combination of a new director, a new building and new teams, the project appears to be more than promising and is expecting to build up a young and strong research community over the next five years.

4 • Team-by-team analysis

Team 1 : Immunotargeting and Radiobiology in Oncology

Name of team leader: Mr André PÈLEGRIN

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	6	2
N2: Permanent EPST or EPIC researchers and similar positions	6	3
N3: Other permanent staff (without research duties)	4	3
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	1
N6: Other contractual staff (without research duties)	3	2
TOTAL N1 to N6	**22**	**11**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	6	
Theses defended	12	
Postdoctoral students having spent at least 12 months in the unit	6	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	9	4

• Detailed assessments

Assessment of scientific quality and outputs

Team 1 has a long-standing and strong expertise in immunotargeting for cancer therapy. This expertise includes designing, developing and understanding the mechanisms of the action of therapeutic antibodies and conducting translational projects in strong interaction with physicians and industrialists. Subgroup 1, dedicated to therapeutic antibodies, has demonstrated that dual EGFR/HER2 monoclonal antibody therapy has a synergistic effect on pancreatic cancer, a combination that is currently being tested in clinical trials at the ICM Cancer Hospital. They have also developed patented antibodies directed to second-generation targets (anti-HER3, anti-Axl, anti-TfR1, anti-MISRII antibodies) which are currently being evaluated in pre-clinical or clinical studies. Subgroup 2, dealing with the radiobiology of external radiotherapy, has developed and is now evaluating a biological test that identifies patients at risk of developing severe late fibrosis after radiation. Sub-group 3, devoted to radio-immunotherapy, has demonstrated the in vivo efficiency of mAbs labeled with Auger electron emitters in peritoneal carcinomatosis after intraperitoneal administration.

The research carried out by team 1 can be qualified as very good. Between 2008 and 2013, team 1 published 82 research articles including 27 as first or corresponding/senior author in the field of molecular and cellular oncology, nuclear medicine and radiology and radiobiology. The most significant publications of Team 1 during the 2008-2013 period appeared in JCO, Lancet Oncology, Clinical Cancer Research for clinical research, and Oncogene, Neoplasia, Breast Cancer Research and J Biol Chem for experimental research. They also contributed to 31 collaborative articles and published 18 review articles and book chapters.

Assessment of the unit's academic reputation and appeal

Team1's director is the current IRCM director, and is also Deputy Coordinator of the Laboratoire d' Excellence "MAb Improve", in which other members of team 1 are leaders or co-leaders of WPs. This Labex was awarded to quite a few teams of very high visibility in the field of oncology in France. All the team researchers are involved in this LabEx, which is focused on the team's main scientific activity (development and improvement of novel therapeutic antibodies for cancer). Several members of team 1 are also active members of the SIRIC "Montpellier Cancer" and one researcher is WP leader of the RadioToxicity FP7 consortium.

This team is fully integrated to the next "Therapeutic Antibodies" program of IRCM.

The team's PI and members are regularly invited to give lectures (30 invited conferences), mainly in France.

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

The research topic of the team is of major relevance to the INSERM's missions and importance for public health.

Several members of the team participate to scientific committees in the field of immunotargeting and cancerology at both national (Ligue nationale contre le cancer, canceropôle) and international (Italian cancer association, Israel science foundation) levels. They are also members of editorial boards (Mabs, JCO, Radiation Oncology, current Radiopharmaceuticals…).

Ten patents were submitted during the 2008-2013 period and 2 are under licence. A start-up SurgiMab for which Team 1's director is a consultant has been incubated by the team since its inception and has three employees. During the period evaluated, they obtained more than one million euros (from academic and industrial sources) which permit the development of costly research.

They have been participating in the design and development of two websites for public and health professionals dedicated to cancer.

This team is mainly involved in clinical projects (4 PHRC, 2 clinical trials). One member was interviewed by national TV channels about the test this team developed to detect patients at risk of severe fibrosis after radiation.

Assessment of the unit's organisation and life

The team leader is the current director of IRCM and the team's staff is very well structured within distinct research themes centered around the above depicted team's main focus.

Assessment of the unit's involvement in training through research

The team has made many contributions to lecturing duties at the University level. The team includes 3 Professors and assistant-professors and all other members are regularly involved in lecturing at Master level in different universities and on specialization courses (DESC, DU, DIU). They designed and are coordinating an international master program on cancer biology.

Twelve theses have been defended during the period and all PhD students are currently employed in academic institutes or biotech companies. Six theses are currently under preparation.

Assessment of the strategy and the five-year plan

The proposed four sub-projects are in the direct line of the research programs carried out over the last six years, and are now focused only on Therapeutic antibodies and Radiobiology applied to external radiotherapy. Radioimmunotherapy will run independently, as a new and separate program hosted by the "Translational Research Unit" that will be created at the ICM in conjunction with by IRCM.

Concerning the Therapeutic antibodies axis, the target antigens, the pathologies studied and the strategic choices remain unchanged with at each time molecular, pre-clinical and clinical phases of study of the antibody of interest or of a combination of targeting antibodies. The projects are well focused, important and feasible. Although immunotargeting in Oncology is a competitive field of research, especially concerning anti-HER antibodies, this is clearly not a program at risk. The researchers have adopted a wise strategy by developing projects on niches (targets or types of cancers) which guarantee their place at international level.

The involvement of a radiotherapist in the Radiobiological axis is key for the clinical transfer of the team's discoveries and the research on the predictive test of tissue response to radiotherapy is very important for the clinical practice. Nevertheless, this latter subject appears somehow on the fringe of the team's main line of research and projects combining targeted therapies with radiotherapy should be developed in the coming years.

Overall, the global strategy and 5-years project of team 1 are judged excellent.

Conclusion

- **Strengths and opportunities:**

Relevance of the research project for IRCM and the hosting institutions;

Skills and experience in the proposed project;

Wise balance between sub-projects concerning the already validated targets of recognized therapeutic interest (anti-HER family antibodies). Due to strong international competition the team has adopted a niche strategy by focusing on the development of antibodies against original targets in less frequent cancers (antiTFr1 and antiMISR-II; pancreatic carcinoma, ovarian cancers…).

The team has an excellent national attractivity and visibility through major national grants (Labex, Siric);

There are numerous industrial connections (patents, licences, contracts).

- **Weaknesses and threats:**

Few collaborations with molecular immunology teams;

Level of international collaboration could be raised;

Lack of publications in outstanding journals;

Risk of international competition on the same mAb targets.

- **Recommendations:**

To maintain the current rate of scientific production of the group, and increase the impact factor of targeted journals;

To increase international collaboration and networking;

To strengthen the TfR1/CD71 project, i.e. by focusing on the most promising antibodies and increasing the staff involved.

Team 2: Functional screening and targeting in cancer

Name of team leader: Mr Pierre MARTINEAU

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	2	4
N2: Permanent EPST or EPIC researchers and similar positions	4	3
N3: Other permanent staff (without research duties)	4	3
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	
N6: Other contractual staff (without research duties)	2	
TOTAL N1 to N6	**14**	**10**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	7	6

• Detailed assessments

Assessment of scientific quality and outputs

The team as a strong exertise in the field of cancer cells and tumor resistance to treatment using imaging mass spectrometry (IMS) and antibodies. The main aim of its work is to identify new therapeutic targets and drugs. To this purpose, the team has developped original animal models of head and neck tumors. The team has been highly innovative in several fields such as intrabody technology (intrabodies libraries, intrabody based phenotypic screening…), imaging tumors using MALDI-TOF (especially oxaliplatin and derivatives). The team has published a good quantity of publications on the past 5 years in journnals of good to very good quality (Plos One, Autophagy, Cancer Res…) and in excellent journals in collaborative works (Nat. Comm., Nat Med.)

A very good team with a highly specialized profile.

Assessment of the unit's academic reputation and appeal

The team is renowned in the field of tumor immunology and resistance. In the future unit, the team will be splitting into two independent teams which will probably increase the visibility of both groups. The team has proven its capacity to raise consequent fundings through national agencies, industries and charities organization. Members of the team are regularly invited to give seminars and oral presentations in national meetings and the team is a founding member of the Labex MabImprove.

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

Team 2 has a strong potential of valorisation with several patents and one with license. 2 projects have ongoing strong industrial partnerships:

-with Sanofi-Aventis on intracellular phenotypic screening for drugs in allergy and inflamation, and

-with a start up (BioXTal) for the development of intrabodies libraries.

Assessment of the unit's organisation and life

See general comments on the IRCM.

Assessment of the unit's involvement in training through research

Several members of the team are in charge of teaching in Université de Montpellier (Master 1 and 2). 8 PhD and 16 master students have been trained in the past 5 years

Assessment of the strategy and the five-year plan

The scientific project will be developed along 2 main axis:

-functional screening using intrabodies and

-targeting residual cancer cells. It is mostly a technological development project. It is a continuation of the work of Mr Pierre MARTINEAU and his group.

The objective is to identify new targets and from this to develop drugs (chemical or biological molecules) and to minimize the time from characterisation of antibody to animal testing.

I) Theme 1: functional screening using intrabodies. Considerable amount of work made by the team has overcome the main problem with intrabody technology: poor expression and/or intracytoplasmic unproper folding of the antibody. Using this approach and new generations of intrabodies library, they will target the different isoforms of the tyrosine kinase Syk in breast cancer and colon cancer. Other tyrosine kinases with cancer specific post-translational modifications are also putative therapeutic targets. The team plans to make “a la carte” libraries against some of them. This will lead to collaboration with different teams outside and inside the IRCM.

II) Theme 2: targeting residual cancer cell. The ongoing work on the molecular characterization of cells with antibodies and mass spectrometry will be continued and implemented. Phage display and MS technologies to isolate and characterize antibodies of interest will be developed to select the more resistant cancer cells both in cell lines and in patients samples.

Conclusion

- **Strengths and opportunities:**

The collaboration with industrial groups and the capacity to develop “applied” projects.

An unique expertise in intrabodies and a strong one in IMS.

The project is an original approach on cancer resistance to treatment.

- **Weaknesses and threats:**

Very good publications in collaboration but not as good for original publications. The team should be careful to not become only a “collaborative technological” team.

International competition is very high and the group deserves a better recognition.

The team leader is the proposed deputy director. It should be detrimental for him if this new administrative function hampered his involvement in the scientific work of the team.

- **Recommendations:**

This is a very good group, with well-designed technological projects. However, the basic aspect of the studies should be more focused and the collaboration between the two main themes of the team should be also maintained and even re-enforced.

Team 3: Immunity and Cancer

Name of team leader: Ms Nathalie BONNEFOY

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	3
N6: Other contractual staff (without research duties)	1	1
TOTAL N1 to N6	**7**	**9**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students		
Theses defended	7	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	4	4

• Detailed assessments

Assessment of scientific quality and outputs

This is a newly assembled team with 3 scientists and 1 physician originating from diferent institutions. The team as such is a "junior" team at the IRCM since september 2012. However, the team members have complementary expertise and domains of interest. This almost unique combination should provide interesting and important outputs on the study of relationships between tumor cells and immune surveillance effectors.

Assessment of the unit's academic reputation and appeal

The team leader is a renowned scientist in the field of tumor immunology and apoptosis and recently has moved from Lyon to Montpellier. Other team members are either specialists of immunotherapy or immunopathology with excellent reputations. The team has been reinforced by 2 post-docs and 2 PhD students which proves an important "appeal". For the moment, the main financial supports are provided by pre-industrial or biotechs funding agencies. The team is a member of Labex Mab-Improve and The Carnot institute Calym.

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

Team 3 has a strong potential of valorisation with ongoing projects which have strong industrial potential with 7 patents including one licensed. Teams members are co-founders of Orega Biotech which has been awarded collaboration contracts with INSERM.

Assessment of the unit's organisation and life:

See general comments on the IRCM.

Assessment of the unit's involvement in training through research

Several members of the team are in charge of teaching at the Université de Montpellier (Master 1 and 2) and one member is a full professor at the school of medicine.

Assessment of the strategy and the five-year plan

The scientific projects will be developed following 2 main axes. The first one is dedicated to the role of Bcl-2 antiapoptotic proteins in cancer (theme 1). It is a drug development project. It follows the work carried out for many years by an investigatoron the Bfl-1 anti-apoptotic protein in autoimmune diseases and cancer and should end up with the discovery of new Bcl-2 family inhibitors targeting Bfl-1.

The objective is to develop drugs that could inhibit BFL1 function to increase sensitivity to conventional chemotherapy in haematological malignancies or solid tumors.

The second research axis is focus on the analysis of immune tumor microenvironment The work will involve:

A. Tumor microenvironment:

- Regulation of gamma delta T cell effector functions;
- Role of CD39/CD73 ectonucleotidase and adenosine pathway in tumor immune tolerance;
- Pro-oncogenic effect of IL-17 cytokines.

B. Immunomodulatory mechanisms of therapeutic monoclonal antibodies

The work on IL-17 investigates whether some isoforms could enhance tumor proliferation or chemoresistance or metastasis (such information is new and important). The study of the role of gamma delta T cells in tumor infiltrates will bring new and interesting information on tumor immune response.

Conclusion

- **Strengths and opportunities:**

The collaboration with industries and the immediate possible application of the projects.

A unique combination of expertise.

- **Weaknesses and threats:**

Most financial support was obtained from industrial partners and with impact on the capacity to develop basic science.

The team is small and the usage of both human and mice model will be a risk of dispersion.

International competition is very high and the group should probably focus on one or two projects only.

- **Recommendations:**

This is a very good group. They should be focusing more on the basic aspect of their studies and also narrow down the themes and/or increased collaboration between the different themes.

Team 4: Drug resistance and new cancer therapies

Name of team leader: Ms Céline GONGORA

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	3	4
N3: Other permanent staff (without research duties) :	4	5
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**8**	**11**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	4	
Qualified research supervisors (with an HDR) or similar positions	5	5

• Detailed assessments

Assessment of scientific quality and outputs

Ms Céline GONGORA's team is a new team originating from Mr Pierre MARTINEAU's group. The aim of this team is to study the mechanism of drug resistance in colorectal cancer. The team members have good to excellent publication records. The team is composed of researchers and MDs already present in IRCM and newcomers, a specialist of autophagy, of irinotecan and of pharmacogenomics. The future team will thus have different and complementary expertises which will certainly be a great asset for the study of drug resistance in cancer. Overall, the proposed research group will include 7 senior researchers with permanent positions (4 CR/DR, 3 H/HU).

Overall, the scientific production (N = 61 original publications) includes 19 original papers that have been published in good/very good (Cancer Res., ...) to very good/excellent journals (IF > 10, including 2 Autophagy, 1 JCO). These publications are signed by members of the proposed new team as first and/or last authors. In addition, excellent publications have been produced in collaboration with other groups (1 Nature Med., 1 Nature Com., 1 Mol. Cell). There is no original publication from the team in very-high impact journals however (IF > 20).

Assessment of the unit's academic reputation and appeal

All scientists present in the team have an excellent reputation and are considered as specialists in their domain. However, although the training of PhD students is good, there is a lack of post doctoral fellows in the group.

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

The team has 2 European patents on anti-claudin-1 and some members have been implicated in clinical trials as promoters or as principal investigators. Several team members have received grants from the industry (NOVARTIS, Astellas). The team leader is responsible of the IRCM student committee since 2008.

The team will develop a clinical trial during the next few years.

The teams has strong interactions with industry.

They participate in the SIRIC and Labex MabImprove.

Assessment of the unit's organisation and life

See general comments on IRCM.

Assessment of the unit's involvement in training through research

All members were in charge of students and teaching mostly for master 1 and master 2 students.

Assessment of the strategy and the five-year plan

Research will be focused on colorectal and prostate cancer resistance to conventional treatments and the finding of new predictive biomarkers and drug targets.

This will be developed along the following 3 projects:

I) Theme 1: Role of the MAPK p38 in chemoresistance. The first part will be to identify the cellular mechanisms of p38 in irinotecan resitance, in particular those that are related to apoptosis, autophagy and lipid metabolism. The second part will be to evaluate the combination of irinotecan with p38 inhibitors in the irinotecan resistant metastatic colorectal cancers.

II) Theme 2: new predictive biomarkers, therapeutic targets and combination therapies in CRC. The effect of multiple drug combinations will be assayed against the main CRC subtypes as well as chemo-resistant CRC cell lines both in vitro and in vivo. The targets chosen are PI3K/AKT/mTOR, and MAPK JAK/STAT3 pathways. System biology methods will be used to assess the robustness of the approach before any clinical trials. In parallel, transcriptomic

analysis/ synthetic lethality will be performed to screen for genes involved in chemoresistance either to single or multiple agents. As such the project is highly conjectural and certainly needs to be refined especially

-because of the intense international competition in the field;

-because the question of genetic/clinical tumor heterogeneity in CRC is not enough considered as an important variable in the proposed screening strategy.

III) Theme 3: new predictive biomarkers, therapeutic targets and combination therapies in prostate cancer. First, the interaction between DNA-PKs and TOPO1 and sensitivity to cisplatin derivatives will be studied and new TOPO1 inhibitors will be screened. An in silico approach will be used to identify patients that will benefit of current treatments. In parallel, a pharmacogenomics on SNPs will be performed in prostate cancer patients enrolled in the CABOBS cohort of the "Cancéropole Sud Ouest".

These different studies are of particular interest for CRC and Prostate cancer. The multidisciplinary approach chosen by the team seems to be promising. Note that some members of the team will be involved in several of the themes. This will be important for the cohesion of the projects and the insertion of new researchers.

Conclusion

- **Strengths and opportunities:**

This is a new proposed team composed of groups that have already developed a very good/Excellent translational research activity in the field of colon/prostate cancer. The strong expertise in the field of drug resistance of the "original" team (CRC) will benefit greatly from the arrival of specialists of complementary fields (prostate, autophagy). If the fusion within the team of the different people is successful, this will be a great opportunity to improve the capacity of the team to provide the robust data necessary for clinical studies on drug combinations and personalized medicine.

- **Weaknesses and threats:**

The project needs refinement especially on the go/no go strategic aspects (Theme 2). This new group should be particularly attentive to avoid dispersion. The team should expect high international competition and should seek for more integration to national or international networks.

- **Recommendations:**

More post docs or scientists (hired in the group or in collaboration) will be necessary to reinforce certain aspects of the project (NGS, bioinformatics for example).

Team 5: Proteases, microenvironment and cancer

Name of team leader: Ms Emmanuelle LIAUDET-COOPMAN

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	2	1
N3: Other permanent staff (without research duties)	2	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**5**	**3**

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

• Detailed assessments

Assessment of scientific quality and outputs

The team 5 coordinated by Dr Emmanuelle LIAUDET-COOPMAN has focused his interest on the lysosomal protease cathepsin D and on autophagy. Based on their expertise acquired during the last 5 years on cathepsin D and the tumor microenvironment, the team has extended its research to the functions of secreted cathepsin D during cancer progression and the elaboration of a complex cross-talk between tumor cells and surrounding stromal cells. The group has provided evidence for an unexpected binding of cathepsin D to the LRP1 receptor expressed at the fibroblastic cell surface leading to increased fibroblastic outgrowth in the tumor environment and triggering adipocyte differentiation. Interestingly, it also identified a new substrate for cathepsin D, cystatin, which leads to the inactivation of one of the most potent extracellular cystein cathepsin inhibitor. Notably, the most recent discovery of the team is the nuclear localisation of cathepsin D and its interaction with a transcription (repressor) factor, TRSP1. Although intriguing, this exciting finding is in line with emerging data reported at international meetings that highlight more and more the presence of proteases in the nucleus and their interference with transcriptional activity. Therefore, the group has provided innovative data in the field and their findings open new opportunities.

Despite its small size, the group has generated innovative data leading to good publications in the field. In addition, some very good publications are found in journals with high impact factors in the cancer biology field (FASEB J, Oncogene, J Cell Sci, Journal of Cell Biology).

Assessment of the unit's academic reputation and appeal

Although the team is small, its leader is well recognized in the international community of proteases and tumor environment. Ms Emmanuelle LIAUDET-COOPMAN has established an excellent network of international collaborations in the context of an EU framework program and with experts in the field of proteases and tumor environment such as C. Overall (Canada), Z. Werb (UCSF, USA), T. Reinheckel (Freiburg, DE) and J. Heigh (Ghent, BE). These collaborations have proven their fruitfulness with the identification of a novel substrate of cathepsin D (SPARC) and are generating a new wave of research by the development of transgenic mice and the retroviral delivery of TRSP1 in the mammary tumor cells. Finally, the team leader is an active member of the International Protease Society (IPS).

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

One patent entiteled: “METHODS FOR TREATING AND DIAGNOSING A CANCER SECRETING CATH-D OR ALZHEIMER'S DISEASE” was published on the 09.04.2009. The invention relates to an inhibitor of the interaction between pro-cath-D and LRP1 ß chain and/or of LRP1 expression for the treatment and/or the prevention of a cancer secreting cath-D or of Alzheimer's disease. The presented invention also relates to the use of a fragment of LRP1 as a marker of a cancer secreting cath-D or Alzheimer's disease.

Assessment of the unit's organisation and life

See general comments on IRCM.

Assessment of the unit's involvement in training through research

The team has a direct impact on researcher training by contributing to 4 PhD, 1 master and 1 HDR. Its indirect impact relies on participation as referee in PhD, HDR and thesis committees, as well as by contributing to the life of doctoral school.

Assessment of the strategy and the five-year plan

The team is obviously at an important turning point. Cathepsin D is no more considered as a “simple” lysosomal enzyme and its complexity is emerging. Although its important contribution in breast cancer progression is widely accepted, the mechanisms of its action remain unclear. The objectives of the team have been extensively revised leading to a focus on novel functions of cathepsin D in vivo, without continuing the research on autophagy. This is an

important challenge and the group leader has established collaborations with the best groups in the protease field to achieve her ambitious objectives. They will generate transgenic mice overexpressing cathepsin D and exploit the well known PymT model to investigate breast cancer development. The development of antibodies against cathepsin D is also important for future therapeutic applications. The study of interplay between TRSP1 and cathepsin D, in collaboration with Z. Werb, is well planned and innovative.

Conclusion

Team 5 showed an impressive research activity on the field of proteases, microenvironment and cancer. Despite its small size, the group has generated innovative data leading to good publications in the field. The established collaborations will be extremely helpful to guarantee the success of the well planned research for the next 5 years.

- **Strengths and opportunities:**

The group has excellent international collaborations. This cooperation is underlined by numerous articles published in collaboration.

Team 5 has a unique expertise on cathepsin D.

- **Weaknesses and threats:**

The small size of the team might be a weakness. To overcome this problem, there is a need of additional postdoctoral fellows.

- **Recommendations:**

The recruitment of high profile post-docs may be beneficial for an increased scientific output of team 5 in the future.

Team 6: Signaling of Tumor Invasion

Name of team leader: Mr Peter COOPMAN

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	4	4
N3: Other permanent staff (without research duties) :	2	2
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	6	6

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

• Detailed assessments

Assessment of scientific quality and outputs

This new team directed by Mr Peter COOPMAN (CR1 CNRS) draws together 4 researchers and 1 Oncologist. They have a recognized background and expertise in breast cancer research and treatment. It is composed of (I) an emerging IRCM junior group including 2 researchers and 1 technician; (II) a scientific group coming from the neighboring CRBM/CNRS institute including 2 other scientists; a medical oncologist.

Their aims are to investigate signaling pathways affecting positively and negatively breast cancer invasion and epithelial to mesenchymal transition (EMT). They are combining (phospho)proteomics approaches with high resolution live-cell image analysis, xenografts and transgenic mouse models. The clinical relevance of the data is validated by using human tissue samples. The research is well focused on three regulators (2 tumor suppressors and 1 pro-tumorigenic regulator):

(1) the anti-oncogenic effect of the cytoplasmic tyrosine kinase Syk leading to the discovery of sub-cellular localisations and new substrates (40 new proteins) involved in epithelial cell polarisation and cell-cell interactions. The team also identified Snail, an important regulator of the EMT process, as a repressor of syk in breast cancer cells.

(2) the tyrosine phosphatase PTPL1 whose expression in breast tumors appears as an independent prognostic indicator of a favorable outcome. The team provided evidence that PTLP1 exerts anti-tumorigenic effects through a direct src inactivation by dephosphorylation. Their both clinical and experimental data support the concept that PTLP1 favors cell-cell adhesion and reduces tumor cell invasion.

(3) transcription factor FRA-1 involved in metastatic dissemination. The team members have demonstrated the implication of a new PKC isoform in the regulation of Fra-1 expression and activity (though its phosphorylation). They also showed the role of Fra in cell-cell contact linked to beta catenin localisation in the cell membrane.

Thus, the team is providing new data on signaling pathways involved in breast cancer cell invasion (EMT) that can be sometime extended to colon cancers. The research is well focused with complementary competence between the thee “subgroups”. The recent recruitment of an active medical oncologist (MD/PhD) (7 additional publications) in the team is very important to ensure the clinical relevance of the research conducted.

Since 2008, these scientists have published 8 papers (publications signed as first/last authors) in good cancer research journals (1 Cancer Res., 2 Oncogene, 1 FASEB J, ...). They also published papers in collaboration (N = 6, specialized journals in the field).

Overall, the scientific production is good but limited (number of publications) likely due to the initial small size of the group and does not include publications in high/very-high IF journals.

Assessment of the unit's academic reputation and appeal

Since 2008, these researchers have obtained important grants to support their research activity notably from INCa. Importantly, one of the scientists coordinated the INCa funded network called RésisTH that is composed of 7 research teams and 5 clinical Departments (Funding: 1000 KE from 2007 to 2010). The team leader coordinated an INCa network studying the Syk TK and its role in suppressing breast tumors (239 KE) and is co-participant in another one. Despite a limited number of recent publications (see above), it appears that researchers from the proposed team are highly active to collect financial supports and already have a very good national recognition in their field. Members of the team have been also invited as speakers in national and European meetings. Each researcher is known in his field. The team has now to be internationally recognized as a whole.

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

One of their findings has been recently patented (PLP1, as a biomarker of survival in breast cancer).

They have organized a regional conference in their field.

The team leader is also contributing to communication actions with the Ligue Contre le Cancer and the National Committee for Hygiene and Security of Inserm.

Assessment of the unit's organisation and life

As a new team, its members will have to adapt to collaborate and publish together (putative conflicts of interest will have to be avoided).

Assessment of the unit's involvement in training through research

The team has trained 5 PhD students since 2008. Team members are involved in academic teaching in Montpellier. They are also involved in regional evaluation of science but there is a lack of participation of team members to national or international evaluation committees.

Assessment of the strategy and the five-year plan

For the next five years (2015-2019), this emerging team created in 2012 will be supervised by Mr Peter COOPMAN. After having explored novel functions of Syk, PTLP1 and Fra-1, the team will naturally explore the potential links and convergence between these factors with an obvious special emphasis on the beta catenin pathway involved in EMT and tumor invasion.The project is thus an interesting proposal

(I) to go deeper into the understanding of the role of candidate anti/oncoproteins in breast cancer;

(II) to find out new candidate proteins involved in tumor progression and invasion.

These candidate proteins have been studied for several years by this team (e.g. Syk kinase, Fra-1 and PKCTeta, PTPL1). Of interest, new tools are developed by the team to develop the proposed project, i.e. quantitative (phospho)proteomics, the use of transgenic mouse models (already available in IRCM), a novel automated image analysis-based invasion assay allowing an extensive siRNA screening for the findings of invasion-related target proteins.

Conclusion

It is expected that the association of these 2 groups that both develop a good scientific activity in the field of breast cancer will be synergistic in the future IRCM.

- **Strengths and opportunities:**

Association of 4 staff scientists and 1 oncologist with well-established competence in breast cancer.

Complementary expertise in cell signalling with a strong focus on the same cancer.

The team is already active and PhD students have recently joined the group to develop ongoing projects.

- **Weaknesses and threats:**

Since it involves 4 researchers and 1 MD with HDR, it is expected that the size of the group will increase during the next five years.

Need of postdoctoral fellows.

Low number of recent publications and lack of high to very-high IF publications.

The proportion of master students appears high (15 for a team of 8 researchers)

- **Recommendations:**

Recruit high profiles post-docs to develop the ongoing project and increase the possibility of the team to publish in high/very high IF journals.

Increase the participation of team members in National and International evaluation committees.

Team 7: Epithelial cell proliferation and polarisation

Name of team leader: Mr Alexandre DJIANE

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

Mr Alexandre DJIANE is CR1 Inserm and joined the IRCM through an open call in 2010. He was awarded an Avenir/Atip grant.

He started his avenir/atip team in 2012 and thus formally does not need to be (re) evaluated for the next period. The obtention of the Avenir label is a guarantee of an excellent scientific quality and project. The period covered by the type of grant is 3 +2 years which includes most but not all of the next 5 year term at IRCM.

Assessment of the unit's academic reputation and appeal

The reputation and attractivity of the team is excellent. During his post-doctoral positions, the team leader published in high ranking journals such as Cell, EmboJ, Development, J Cell Biol. He takes advantage of the Drosophila model to understand how proliferation is controlled in epithelial cells by identifying the gene regulatory networks activated by the Notch pathway during epithelial proliferation, and to study the role of epithelial cell architecture on the proliferation potential of epithelial cells. He has already been able to hire a scientist and a technician with permanent jobs at the Inserm plus a post doc and a PhD student. Members of the team have already published important and significant papers in their field. Beside the Avenir / Atip grant, Mr Alexandre DJIANE has obtained a Marie Curie Career Integration Grant in 2013.

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

None

Assessment of the unit's organisation and life

See general comments on IRCM.

Assessment of the unit's involvement in training through research

A PhD student has been hired and scientists have already trained master students.

Assessment of the strategy and the five-year plan

Research themes are divided in :

1. Functional characterization of epithelial scaffolds during cell proliferation and survival.

MAGI-1, a member of the MAGUK family of proteins, is shown to be rapidly cleaved during apoptosis. The purpose of the project is to understand the mechanisms and partners linking MAGIs apoptosis and loss of adherens Junctions. This process, which is fundamental in epithelial polarity, might also be important in cancer progression (EMT, metastasis…). This will be studied in Drosophila models.

2. Understanding the effects of the Notch pathway on epithelial proliferation

The team has studied the implication of Notch signaling in hyperplastic growth. The project will concentrate on the inter-connection between Notch signaling and the loss of epithelial polarity.

3. Cross regulations and integration of cell signaling and polarity

This project will translate results found in drosophila models to mammalian cells and especially cancer models obtained from other IRCM teams. The aim is to find a “Notch signature” for different cellular types.

The research project is highly original and has already led to several landmark studies in the relevant field that have not yet been published. Since their arrival at IRCM, they have already identified new determinants involved in

Adherens Junction homeostasis and cell signaling and survival. These projects are well integrated within the team and open obvious possible connections with several IRCM teams.

Conclusion

- **Strengths and opportunities:**

This is a young team with an excellent project and complementary expertise with other groups at IRCM.

- **Weaknesses and threats:**

Team members have not worked yet on the same research program and published together or worked as independent researchers.

- **Recommendations:**

The integration within the IRCM should be implemented through established common programs with other teams or clinicians.

Team 8: Hormone Signaling and Cancer

Name of team leader: Mr Vincent CAVAILLES

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	2	3
N2: Permanent EPST or EPIC researchers and similar positions	4	4
N3: Other permanent staff (without research duties)	3	2
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	1
N6: Other contractual staff (without research duties)	2	2
TOTAL N1 to N6	13	12

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students		
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	4	4

• Detailed assessments

Assessment of scientific quality and outputs

Team 8 coordinated by Dr Vincent CAVAILLÈS has focused its interest on the nuclear receptor network, how it is influenced by its ligands and how transcription is regulated by the ligand receptor complex. Based on their expertise acquired on nuclear receptors and the tumor microenvironment during the last 5 years, the team has extended its research to the functions of endocrine disruptors that target nuclear receptors. The group has provided evidence for binding of environmental ligands like bisphenol A and benzophenones to ER□, PPAR□ and RARs. Interestingly, team 8 also identified a group of various transcription coregulators of nuclear receptor activity like TRIM24, SENP2, LCoR and RIP140. Notably, the most recent discovery of the team is that ERß expression strongly decreased the mitogenic effect of E2, significantly reduced E2-dependent transcriptional responses (both on a stably integrated estrogen response element [ERE] reporter gene and on E2-induced mRNAs), and strongly enhanced the formation of ER heterodimers in ovarian cancer cells. Although intriguing, this exciting finding is in line with emerging data reported in international meetings that highlight more and more the different roles of ER□ and ER□ in breast and ovarian cancer. Therefore, the group has provided innovative data in the field and their findings open new opportunities. The group has generated innovative data leading to 71 publications in excellent journals in the field during the last 5 years (e.g. Nature Structural & Molecular Biology, PNAS, Clinical Cancer Research, Molecular Cancer Research, Genes Brain and Behavior, PLoS ONE,). In that period, these publications generated 634 citations equal to an h factor of 14.

Assessment of the unit's academic reputation and appeal

The team leader is well recognized in the international community of nuclear hormone receptors and tumor biology. The team has established an excellent network of international collaborations in the context of a variety of research programs and with experts in the field of nuclear receptors such as A. MAI (Rome), L. ALTUCCI (Napoli), E. LEYGUE (Manitoba), M.G. PARKER (London), Y. NAHIMAS (Boston), N. OLEA (Granada), I. PONGRATZ and J.A. GUSTAFSSON (Stockholm). These collaborations have proven their fruitfulness by the investigation of HDAC inhibitors, SRA transcription factors, generation of RIP140 KO mice, investigation of phytoestrogens and ER AHR interference. Finally, Mr Vincent CAVAILLÈS is an active member of American Association of Cancer Research, French Society of Biochemistry and Molecular Biology and the French Society of Endocrinology.

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

Ten bioluminescent reporter cell lines were licensed to companies. HG5LN, Gal4-PPARs, HELN□, HELN□ and HELN AR cell lines were licensed to TEBU-BIO. MELN, PALM, HAhLP and HG5LN Gal4-TRa cell lines were licensed to VigiCell. Two further cell lines are under validation by the European Centre for the Validation of Alternative Methods. In addition, members of the team are actively cooperating with industrial companies. Finally, press releases and videos were produced showing the scientific impact of the team.

Assessment of the unit's organisation and life

See general comments on IRCM.

Assessment of the unit's involvement in training through research

The team trained 5 PhD, 20 master and 6 other students. All PhD students attended at least one international meeting. The members of the team have also heavy teaching activity.

Assessment of the strategy and the five-year plan

The team is obviously very well established in the scientific community. Especially the identification of the transcriptional network driven by nuclear receptors, their ligands and coregulators is an impressive goal. In addition, many environmental agro-chemical compounds can be considered as ligands for hormone receptors. The investigation of ER modulation and PPAR/PXR interaction by these environmental factors is innovative and interesting. In addition, transcriptional coregulators for nuclear hormone receptor signal transduction were investigated in the past. For the

next five years, the functional interaction of RIP140 with ERs is another promising goal. Finally, the function of RIP140 for colon cancer signalling will be analysed. A special focus will be the RIP140 – p53 interaction in changes of cancer cell metabolism known as the Warburg effect that is also very innovative.

Conclusion

Team 8 showed an impressive research activity in the field of nuclear receptors, its coregulators and cancer. The group has supervised numerous students, and obtained major national grants and 10 licenses with companies. The established team and the national and international collaborations will be extremely helpful to guarantee the success of the well-planned research for the next 5 years.

- **Strengths and opportunities:**

The group has excellent international collaborations as evidenced by numerous articles published.

The team has a unique expertise on nuclear receptor signal transduction.

There is an excellent continuum from research activities of the team to industrial/clinical applications.

There is a broad know how within the team to achieve the proposed goals.

There is a strong implication in teaching and PhD supervising.

- **Weaknesses and threats:**

PhD students should be hired.

The number of international collaborators could be enhanced.

- **Recommendations:**

There is no special recommendation other than to avoid scientific dispersion as the team is performing very well on all grounds.

Team 9: Molecular basis of carcinogenesis

Name of team leader: Mr Laurent LE CAM

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	2
N6: Other contractual staff (without research duties)	1	1
TOTAL N1 to N6	**6**	**7**

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

• Detailed assessments

Assessment of scientific quality and outputs

This young team directed by Mr Laurent LE CAM has emerged from an AVENIR Junior Group created in 2008. It is composed of 1 DR2, 2 CR and 1 technician. It also includes 2 post-Docs, 3 PhD and 2 AI (CDD). Its research activity has been focusing on molecular pathways involved in aging and carcinogenesis, with a particular interest in new original regulatory mechanisms of the p53 axis in senescence and stem cell functions involving E4F1 and MDM2. They are in the continuity of excellent papers previously published by members of the group in the field before 2008 (e.g. Cell 2006, when they were attached to the team of Mr Claude SARDET). Most projects are based on the use of original mouse models. There are only few recent original publications from their research activity (N = 2) whose level remains however very high in term of IF (J Exp Med 2011; PNAS 2010).

Assessment of the unit's academic reputation and appeal

The team is recent but has already acquired a national and international visibility in the highly competitive p53 research field. They have notably obtained important fundings since 2008 through ongoing collaborations with the team of Mr Claude SARDET (ANR Blanc 2012-2016) and Mr Charles THEILLET (INCa libre 2012-2016) within IRCM. The team belongs to the Labex 'Epigenmed'.

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

The team leader is very much involved in the loco-regional scientific life, playing a crucial role in organizing the core facilities dedicated to animal models in Montpellier: he is the current scientific head of the experimental histology network of Montpellier (RHEM). He plans to head a platform that will include all animal facilities in Montpellier (RAM). He engaged a partnership with a private company (CCITI-Novacyte). He is one of the organizers of the French 'Club des Belles Souris'. In addition, the team co-developed a software that is dedicated to the anatomo-pathological analyses of animal models together with the company CCITI-Novacyte.

Assessment of the unit's organisation and life

See general comments on IRCM

Assessment of the unit's involvement in training through research

The team has developed strong links with l'univsersité de Montpellier and scientific community through teaching, training and organization of core facilities (see above).

Assessment of the strategy and the five-year plan

The project is a follow up of the recent activity of the team to address questions related to the importance of the p53 pathway in regulating energy metabolism and its implication in normal tissue homeostasis, aging and cancer development. A special focus will be the E4F1 - p53 interaction in changes of metabolism in stem cells that is also very innovative. It is very ambitious but seems to be feasible given the excellent scientific background and expertise of team members in engineering mouse models and analyzing their phenotype.

Conclusion

Team 9 showed an impressive research activity and is a very good and highly dynamic young team within the new IRCM. The group has supervised 27 students, obtained 18 national grants and 10 licenses with companies

- **Strengths and opportunities:**

Excellent background and recognized expertise of the team in developing and analyzing pertinent and original mouse models in their field.

High IF level of recent publications even though their number is low.

Originality of their recent scientific work in a highly competitive field of research.

The crucial local role of Mr Laurent LE CAM in the organization of core facilities dedicated to animal models in Montpellier.

- **Weaknesses and threats:**

It is likely that the past but also the recent activity of the group is still highly mixed with the one of Mr Claude SARDET (the recent publication in J Exp Med. is signed as first author by a PhD student whose thesis is co-directed by Mr Laurent LE CAM and Mr Claude SARDET. The main recent funds have been obtained in collaboration with the group of C. Sardet).

What is the real autonomy of this group at both the scientific and financial level in this context when Mr Claude SARDET becomes the head of the future insitute ?

No scientific production and collaboration of the group with other scientific teams outside Montpellier

The absence of clinicians within the team certainly prevents the group to move to the clinics (cancer, aging).

Too many unpublished results.

- **Recommendations:**

Increase the number of HDR within the team to facilitate the welcome of M2/PhD students.

Welcoming of high profiles post-docs to develop the on-going project.

Increase the links with pathologists and clinicians in Montpellier but also at the National/International levels to evaluate the relevance of recent and future findings with cancer and Aging, if this aim is maintained in the proposed project.

Develop projects with other international groups in the field to increase the number of publications in collaboration besides the ones that are originally produced by the team.

Publications are on the way and this must be given the highest priority.

Team 10: Genetic and phenotypic plasticity of cancer

Name of team leader: Mr Charles THEILLET and Mr Claude SARDET

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		1
N2: Permanent EPST or EPIC researchers and similar positions	4	5
N3: Other permanent staff (without research duties) :	3,5	3,5
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**7,5**	**9,5**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	4	5

• Detailed assessments

Assessment of scientific quality and outputs

Team 10 is a merger of two excellent teams in the field of breast cancer, genetic heterogeneity of cancer and phenotypic plasticity of cancer cells. Their field of research is of the uttermost importance and relevance to IRCM and its hosting institutions. Their scientific output was considerable on the five themes. Mr Charles THEILLET 's theme 1 led the team to create a highly valuable collection of patient-derived xenografts (PDX) as a tool for several in vivo studies of breast and also for ovarian cancer presently ongoing at IRCM and elsewhere. Theme 2 was devoted to reducing the heterogeneity of breast cancers into discrete biological entities thanks to their distinct oncogenic cascades, progressions, and genomic profiles, while Theme 3 delineated their phenotypic plasticity and stemness. Mr Claude SARDET 's theme 4 defined novel cancer targets through synthetic lethality studies of E4F1 control of checkpoints and metabolism, in collaboration with Mr Laurent LE CAM's team. Mr Claude SARDET 's theme 5 investigated the regulation by protein methylation of the control of cell proliferation differentiation and genome stability, in collaboration with Mr Eric JULIEN 's lab. The scientific production of Mr Charles THEILLET's and Mr Claude SARDET 's groups over the last period encompasses a total of 70 publications in journals of good to excellent impact factors, including 1 Nature Cell Biology, 1 J. Exp Med, 1 PNAS and 1 Cell Death & Diff… Together, the knowledge and tools (most notably the PDX collection) produced by each of these constitutive teams are a major asset to this unit. Hence, the production and scientific output of this team as a whole is excellent.

Assessment of the unit's academic reputation and appeal

The PI are members of the Laboratoire d' Excellence “Epigenmed", and members of the SIRIC "Montpellier Cancer". This team's reputation and attractivity is excellent at the national and international level. The team's PIs and members are regularly invited to give lectures and conferences in France and at the international level. Several national scientific prizes have been awarded to the team leader.

Together, the team's visibility and attractivity are excellent.

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

The research topic of the team is of major relevance to the INSERM 's missions and importance for public health. The PI is advisor of the current French government for research on cancer, members of AERES jurys and both PIs are members of the major French funding agencies and organizations on cancer research and care. The members of the team participate to scientific committees in the field of cancer research at both national (LNCC, ARC, canceropôle GSO) and international organizations levels. They are also members of several editorial boards.

Several patents on PDX are pending. This team is involved in 3 clinical trials on breast cancer.

These elements indicate that the team's interaction with environment are at an excellent level.

Assessment of the unit's organisation and life

Team 10’s co-PIs are the current IRCM co-director and future IRCM director. They have a major involvement in the current IRCM organisation and life. Furthermore, the team's staff is very well structured within distinct research themes centered around the above depicted team's main focus.

Assessment of the unit's involvement in training through research

During the 2008-2013 period, numerous thesis have been defended and a high number of PhD student are in the current joint group. The team has made and currently does many contributions to lecturing duties at the University level. The team includes Professors and assistant-professors and all other members are regularly involved in lecturing at Master level in different universities and on specialization courses (DESC, DU, DIU). They designed, contribute and are coordinating teaching programs of Ecole Doctorale on cancer biology.

Assessment of the strategy and the five-year plan

The strategy is based on the organisational merge of two former groups, namely Mr Charles THEILLET 's and Mr Claude SARDET 's. Their common 5 years plan comprises two projects: project 1 aims at reducing the heterogeneity of breast cancers into discrete biological entities thanks to their distinct oncogenic cascades, progressions, and genomic profiles using omics approaches, while project 2 will enlarge the current PDX collection that the team formerly generated, in the aim of their use as models for in vivo studies by IRCM and other national teams. This straightforward plan is highly coherent with former scientific production of the team and wise in terms of perspectives for oncology in the major contexts of breast and ovarian cancers.

Overall, the global strategy and 5-years plan of team 10 are excellent.

Conclusion

An excellent project for the scientifically coherent merge of two formerly excellent teams. Its current strategy and 5-year plan are excellent and quite central to the promising development of the global IRCM project.

- **Strengths and opportunities:**

Relevance of the research project for IRCM and the hosting institutions.

Highly dedicated and renowned PI.

Skills and experience of the merged team's staff.

The current integrated project and tools are a major asset to IRCM.

- **Weaknesses and threats:**

Relatively few PhD students in the current lab.

Few international collaborations.

Risk of difficult merge around the common project by staff from each previous teams.

Dispersion due to seemingly different projects of the two team leaders.

- **Recommendations:**

To take care of the successful scientific merge of the involved staff; this could be difficult to achieve because the two team leaders are seniors and do not have the same experience of the IRCM environment.

To benefit of its PDX collection, the team should increase international collaboration and impact factor of targeted journals.

Team 11: Fragile sites, checkpoints and cancer

Name of team leader: Mr Arnaud COQUELLE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties) :	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	2
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**4**	**5**

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

• Detailed assessments

Assessment of scientific quality and outputs

This team has been established in 2011. The team leader has a good scientifc production in the past years (4 publications as co-author since 2009 including a paper in Nat Cell Biol). However his production as senior author is moderate. The research on DNA damage response is close to that developed by other teams of the IRCM and difficult to delineate from that conducted in the lab he collaborated with for the Nat Cell Biol paper.

Assessment of the unit's academic reputation and appeal

The international visibility of the team and especially the team leader seems to be very limited. However, locally, the team has a good interaction with local programs (SIRIC, GSO..) and has already attracted several students and scientists.

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

In the past, the team leader has obtained several patents. However nothing specific is mentioned for the recent past on research based on the actual project.

Assessment of the unit's organisation and life

See general comments on IRCM.

Assessment of the unit's involvement in training through research

The team has already attracted several students.

Assessment of the strategy and the five-year plan

The project is a follow up of the ongoing project which has so far produced no publications. This project seems redundant with several other IRCM projects or too connected with other groups in Montpellier. Clearly the limited amount of persons implicated in the project is a severe restriction. The committee failed to find a clear strategy both in the written report and the talk.

Conclusion

The project needs to be refined and better organized. The need of technical support and mentoring from other scientists seems to be needed.

- **Strengths and opportunities:**

Relevance of the research project for IRCM and the hosting institutions in the cancer fields.

- **Weaknesses and threats:**

Too few international and national collaborations

No well designed and focused projects.

- **Recommendations:**

The team needs to reinforce the team's international visibility by publishing its results.

However, the committee thinks that this team should find a partnership with other groups of the IRCM (or elsewhere) to strengthen both its "taskforce" and refine its scientific project.

Team 12: DNA damage response

Name of team leader: Mr Bijan SOBHIAN

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

N/A : new Junior team joining the IRCM.

Assessment of the unit's academic reputation and appeal

N/A : new Junior team joining the IRCM.

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

N/A : new Junior team joining the IRCM.

Assessment of the unit's organisation and life

N/A : new Junior team joining the IRCM.

Assessment of the unit's involvement in training through research

N/A : new Junior team joining the IRCM.

Assessment of the strategy and the five-year plan

The group leader has just been selected through a recent call for proposal from IRCM, and the research group is currently setting up. The PI itself has published pioneering work on transcription elongation during his post-doc. Two post-docs, including one with a great expertise in the DNA damage response field have been recruited since his integration in the current IRCM profile.

The project contains two parts, one with a clearly identified working plan dealing with the role in DNA damage response of a known protein, which is relocalized to the nucleus upon DNA damage induction. The PI wants to characterize its role in transcription of specific genes following DNA damage induction by up-to-date approaches. This part of the project is somewhat risky however, given the absence of functional data on the involvement of the protein of interest in the DNA damage response. In a second part of his project, the PI proposes to identify all genes transcriptionnally modified upon DNA damage induction in order to find new players in the DNA damage reponse. Since no specific focus is announced prior to undertaking this topic, high is the risk that many options could emerge from the high number of genes fulfilling the criterion of being significantly up or down-regulated upon DNA damage. So, the rationale for the choice of candidates that will be finally characterized in depth has to be clarified from the beginning of the screen for building on a fully rationalized approach, and thus a project likely to reach (some of) its objectives.

Altogether, the committee believes that the project still has to maturate and would strongly benefit from interacting with an expert in the DNA damage response.

Conclusion

- **Strengths and opportunities:**

The PI is an expert in the field of transcriptional regulation and biochemistry.

Two post-docs have already been recruited.

Collaborations within IRCM have been launched.

An installation grant has been obtained.

- **Weaknesses and threats:**

A currently immature project.

Several unclear or not finalized aspects of the projects.

Uncertain management maturity.

Strong threats from a highly competitive field.

- **Recommendations:**

The proposed research plan should be strengthened by the merging of the group with a larger and more established group. In addition to reaching a critical size, such a possibility would provide the young PI with adequate mentorship such as to ensure success in his endeavours and effective realizations.

Team 13: Epigenetic, cell Differentiation and Cancer

Name of team leader: Ms Florence CAMMAS

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	1	2
N3: Other permanent staff (without research duties) :	0,5	0,5
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	2
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	2,5	4,5

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

• Detailed assessments

Assessment of scientific quality and outputs

The group has been created in 2011 following the selection of the group leader, presently CR1 CNRS, through an IRCM call for group leaders. She has an excellent track record from her previous position, with ten original publications published in very good to excellent journals, including one as first co-author in Nature (2012) and two as senior author (Dev Biol 2011 and Mol Biol Cell 2009). Her work was pioneer in the field of investigating the function of transcriptional corepressors and HP1 in mice, and the mouse models she created are now widely recognised and used throughout the world.

Assessment of the unit's academic reputation and appeal

N/A : new Junior team joining the IRCM.

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

N/A : new Junior team joining the IRCM.

Assessment of the unit's organisation and life

N/A : new Junior team joining the IRCM.

Assessment of the unit's involvement in training through research

N/A : new Junior team joining the IRCM.

Assessment of the strategy and the five-year plan

The main topic of the group deals with the function of transcriptional corepressors and HP1 in mice, and its research projects are the continuation of past work, with emphasis on liver pathophysiology. The group will make a strong use of mice models in line with previous work from the group leader, and this is really a strength of the proposal. The proposed approaches include the large use of genome-wide technologies and other up-to-date technologies, which is a bit hard to manage but probably required since the mechanims involved are dificult to predict. Given that the competition on this subject is very strong, the availability of mice models and the expertise of the group leader on these models will provide the group with a clear advantage. However, the relevance of the work to human cancers has yet to be established. In addition, the use of in vitro systems should probably be limited to mechanistic studies in close relation with in vivo findings.

Conclusion

- **Strengths and opportunities:**

The group leader is very experienced and renowned in the research field of the proposal.

The group will make a large use of original and relevant genetically modified mice strains, that will ensure competitiveness.

The group has obtained many competitive grants and has succeeded to reach a critical size.

The arrival of an experienced researcher on a permanent position and with an excellent track record is clearly an opportunity.

- **Weaknesses and threats:**

The development of the group projects has been hampered by difficulties in recruiting PhD students, post-doc scientists or more experienced scientists on permanent positions.

- **Recommendations:**

The group leader has to take care of maintaining a critical size of the group, which is required in this highly competitive field.

A strong expertise on liver pathophysiology is required to develop the project and should be maintained and increased through existing collaborations.

Team 14: Biology of Lysine Methylation and Cancer

Name of team leader: Mr Eric JULIEN

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

This young promising team is led by a group leader that has joined CNRS in 2005 in the group of Mr Claude SARDET and has started an independent group thanks to a ANR Young scientist grant in 2009. The group is composed of 2 stable position researchers (CR1 and CR2) and a starting PhD student. During the period 2008-2013, a major publication validated the work of the team (Nature Cell Biology, 2010, position 7/7). In this publication the team showed the involvement of the protein PR-Set7 (H4-K20 methyltransferase) in the regulation of replication origins in mammalian cells. During this period the PI co-signed an EMBO reports paper (2008) position 2/7 and published a review in Trends in Cell Biology (2011) position 5/5. The main publication of this period has been extensively cited in the field and mentioned in several highlights in 2 high impact journals (Cell and Nature Genetics).

Assessment of the unit's academic reputation and appeal

Because the team is young, it is difficult to appreciate the academic attractiveness. Nevertheless, the PI was able to raise the funding necessary for setting up his own group and collaborated in different national grants in which he is not the coordinator. The PI is a member of several research networks and is regularly invited to give seminars. The PI is also solicited to review numerous national and international grants and scientific manuscripts (IF <10).

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

N/A : new Junior team joining the IRCM

Assessment of the unit's organisation and life

N/A : new Junior team joining the IRCM

Assessment of the unit's involvement in training through research

The PI co-supervised 2 thesis and 2 Post-Doc fellows and was invited to participate in 5 PhD thesis committees, nationally and internationally. The PI participates to Master examination committees and has a certain amount of teaching (30 h) at the université de Grenoble.

Assessment of the strategy and the five-year plan

The team project is focused on three research axes:

The first axis consists in disclosing the role of H4-K20 methylation in tumorigenesis and particularly in breast cancer. The working hypothesis is solid and it is based on results already obtained by the team showing that the differential expression of the histone methyltransferase PR-Set7 can drive the transformation potential. With techniques mastered by the team, such as ChIP sequencing, the focus will be set into mapping the H4-K20 methylation in the overall genome of different tumor graft lines. A second axis is focused on unraveling the mechanism by which H4-K20 methylation regulates DNA replication and maintains genome stability during the cell cyle. The PI is interested in identifying and characterizing the H4-K20 methyltransferase complexes and has set up the tools to develop this project.

The third axis revolves on the study of the Malignant Brain Tumor (MBT) domain proteins in development and cancer. For this project the team will make use of Drosophila as an in vivo model. The expertise in Drosophila development is readily available in the team and the genetic and biochemical tools have also been produced.

Different collaborations are set up within the IRCM to ensure the good development of the project.

Conclusion

- **Strengths and opportunities:**

The techniques are mastered by the team members and the project aims are solid and realistic. When tools or techniques are not available within the team, collaborations are set up within IRCM teams to be able to find the different expertises needed for the good progression of the project.

- **Weaknesses and threats:**

The main weak point is the lack of PhDs, Post-Docs and technicians. On each research axis the PI needs to hire PhDs and Post-Docs. Nevertheless the difficulty in recruiting PhD students is not specific to this team but seems to reflect a general problem in université de Montpellier. Hopefully, because the PI managed to secure fundings for extra staff, the team will reach a critical mass of people to pursue the projects.

- **Recommendations:**

The team might for the first years focus on a limited number of questions on axis 2 and 3 and wait to develop the full project when a larger number of team members will be recruited.

Team 15:

Integrative cancer research for personalized medecine in digestive oncology

Name of team leader: Mr Marc YCHOU

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		4
N2: Permanent EPST or EPIC researchers and similar positions		3
N3: Other permanent staff (without research duties) :		2
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		3
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6		12

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

• Detailed assessments

Assessment of scientific quality and outputs

Team 15 is a new team focused on gastro-instestinal oncology. It is composed of 12 investigators with complementary expertise (MD/PhD, PhD, pharmacists, biostatistician) in basic and clinical cancer research. Individually, the investigators have contributed to the study of colorectal cancer (CRC) biology and to clinical studies aimed at improving the diagnosis and treatment of CRC. The team contributed to and/or coordinated large academic multicentric clinical trials (including phase III clinical trials). Taken together, team members have contributed to 120 publications with 6 in journals whose impact factor is higher than 7.

Assessment of the unit's academic reputation and appeal

Individually, members of the team have collected important grants to support their basic and clinical researches. The director, Mr Marc YCHOU is actively contributing to translational research and numerous clinical trials. He has coordinated phase III clinical trials and is coordinating INCa-supported translational study on biomarkers of chemoresistance in CRC, as well as industry-granted studies. Notably, he is the director of the Integrated Cancer Research Site (SIRIC) Montpellier Cancer. He contributed to the Canceropôle GSO as director and has organized local or national meetings on Gastrointestinal Oncology. Other members are owners of scientific prizes.

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

Contribution to several guidelines (or SOP) and 4 patents.

Creation of a biotech company (DiaDx).

Participation to and coordination of numerous clinical trials.

Assessment of the unit's organisation and life

This is a new team in which the investigators will have to learn to work together.

Assessment of the unit's involvement in training through research

The team has contributed to the training of 10 PhD thesis during the last 5 years. Members are active in teaching at the Faculty of Medicine, Faculty of Pharmacy, Doctoral school.

Assessment of the strategy and the five-year plan

The team objective is to increase the knowledge on CRC cancer biology and identify new predictive markers in order to drive personalized therapeutic strategies. This is a large but nonetheless feasible project that will be certainly successful due to the clinical connections of the team.

Conclusion

The team members have generated important clinical data and are well positioned to conduct translational and clinical studies. Their integration in the IRCM is a stimulating opportunity to strenghten basic research in gastrointestinal cancers.

- **Strengths and opportunities:**

The unit is gathering clinicians and researchers including a biostatistician.

Strong expertise in clinical studies.

Focus on gastrointestinal cancers.

The proportion of permanent positions is high.

Key contribution in the Integrated Cancer research Site (SIRIC).

Collaborations with industries.

Combination of basic, translational and clinical studies.

- **Weaknesses and threats:**

The members of this new team have to learn to work together.

The team has now to be internationally recognized as a whole.

Low percentage of researchers at the bench to increase basic research in synergy with the other IRCM teams.

Multiplicity of research topics.

“Spatial spreading” of team members.

- **Recommendations:**

Necessity to attract PhD students and post-docs to complement clinician contributions.

Prioritize topics to optimize the synergy between team members.

Team 16: Lung cancer signaling

Name of team leader: Mr Antonio MARAVER

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

The group has been created in 2013 following the selection of the group leader, recently hired as CR1 INSERM, through the IRCM call for group leaders. Mr Antonio MARAVER has an excellent track record from his previous laboratories, with 20 original publications published in very good to excellent journals, including one as first co-author in Cancer Cell (2012) and co-authorship in Nature 2007 and Cell in 2008, but none as senior author (although he is co-corresponding author on the Cancer Cell publication). He has studied several aspects of cancer biology and genetics with a special emphasis in Notch signaling. His work is highly significant and he has acquired an impressive expertise in different domains including care and use of animal models in cancer.

Assessment of the unit's academic reputation and appeal

N/A : new Junior team joining the IRCM.

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

N/A : new Junior team joining the IRCM.

Assessment of the unit's organisation and life

N/A : new Junior team joining the IRCM.

Assessment of the unit's involvement in training through research

N/A : new Junior team joining the IRCM.

Assessment of the strategy and the five-year plan

Mr Antonio MARAVER wishes to develop in the IRCM a study on the role of Notch pathway in non small cells lung cancer (NSCLC) using pharmalogical tools and (trans)genetic models in murine and drosophila models. In particular, he will analyze the role of gamma secretase and KrasV12 in Notch signaling in lung cancer. This study will lead to test the efficacy of combination therapies between Notch inhibitors and standard or targeted chemotherapies in mouse models. The most successful combination will be tested in tumor graft from NSCLC patients. This is an excellent project which is completely within Mr Antonio MARAVER's expertise and scope.

Conclusion

- **Strengths and opportunities:**

The group leader is very experienced in the research field of the proposal. The group will make a large use of original and relevant genetically modified mice strains, develop Drosophila models and human cancer grafts in animals in collaboration with other IRCM groups. All these features will ensure integration in the institute and international competitiveness.

The group has obtained grants and one post doc has been been hired.

- **Weaknesses and threats:**

This is a small group which needs to grow in the next year by atracting new scientists (post doc or with permanent position) to maintain its competitiveness.

- **Recommendations:**

Similar to other teams with young leaders, a critical size of the group is mandatory and the IRCM should provide technical assistance to this group as soon as possible. Planned and existing collaborations will certainly be fruitful for both the IRCM and the team. The group has not been formally proposed as a team but nonetheless the

committee has judged that although small, this group should be granted a team status. Its integration in the IRCM seems to be easy and it will provide new avenues for the IRCM research. This team should be created maybe still under a junior status with light administrative charge.

5 • Conduct of the visit

Visit dates:

Start: December 3rd 2013, at 08.00 am

End: December 5th 2013, at 01.00 pm

Visit site: IRCM

Institution: IRCM

Conduct or programme of visit:

DAY 1: December 3rd

08h00 – 08h30	Welcome of the Review Group
08h30 – 09h00	Closed-door meeting (Review Group and scientific coordinator for AERES (DS))
09h00 – 10h00	General presentation of IRCM (Mr André PÈLEGRIN) and perspectives (Mr Claude SARDET)
10h00 - 10h15	**Coffee Break**
10h15 – 11h05	Ms Céline GONGORA (Team 4) - Drug Resistance and New Therapies
11h05 – 11h55	Mr Peter COOPMAN (Team 6) - Signaling of Tumor Invasion
11h55 – 12h45	Ms Emmanuelle LIAUDET-COOPMAN (Team 5) - Proteases, Microenvironment and Cancer
12h45 – 13h45	**Lunch**
13h45 – 14h25	Mr Alexandre DJIANE (Team 7 - Team Avenir) - Epithelial cell Proliferation and Polarisation
14h25 – 14h45	Mr Antonio MARAVER (Team to be created) - Lung Cancer Signaling
14h45 – 15h35	Mr Laurent LE CAM (Team 9) - Molecular Oncogenesis
15h35 – 16h25	Mr Charles THEILLET and Mr Claude SARDET (Team 10) - Genetic and Phenotypic Plasticity of Cancer
16h25 - 16h40	**Coffee Break**
16h40 – 17h20	Mr Arnaud COQUELLE (Team 11) - Fragile Sites, Checkpoints & Cancer
17h20 – 18h00	Mr Bijan SOBHIAN (Team 12) - DNA Damage Responses
18h00 – 20h00	Closed-door coordination meeting of the Review Group with the DS (Dr Jean ROSENBAUM)

DAY 2: December 4th

08h30 – 09h10	Mr Eric JULIEN (Team 14) - Biology of Lysine Methylation and Cancer
09h10 – 09h50	Ms Florence CAMMAS (Team 13) - Epigenetic, Cell Differentiation and Cancer
09h50 - 10h10	**Coffee Break**
10h10 – 11h00	Mr André PÈLEGRIN (Team 1) – Immunotargeting and Radiobiology in Oncology

11h00 – 11h50 Mr Pierre MARTINEAU (Team 2) - Functional screening and targeting in cancer

11h50 – 12h40 Ms Nathalie BONNEFOY (Team 3) - Immunity and Cancer

12h40 – 13h40 **Lunch**

13h40 – 14h30 Mr Vincent CAVAILLES (Team 8) - Hormone Signaling and Cancer

14h30 – 15h20 Mr Marc YCHOU (Team 15) - Integrative cancer research for personalized medicine in digestive oncology

15h20 – 16h00 Platforms and URT (Mr Charles THEILLET)

16h00 – 17h00 Parallel meetings:

- with Tenure Researchers, Associate and Full Professors (without the Team Leaders)
- with Technical and Support Staff
- with Students and Post-Doctoral Fellows.

17h00 - 17h20 **Coffee Break**

17h20 - 17h50 Closed-door meeting with the representatives of IRCM Operating Bodies (INSERM, Université de Montpellier) and Partner (ICM).

17h50 - 18h05 Closed-door meeting with the representatives of the Doctoral School.

18h05 – 20h00 Closed-door coordination meeting of the Review Group with the DS (Dr Jean ROSENBAUM)

DAY 3: December 5th

08h30 – 09h00 Closed-door meeting with the present (Mr André PÈLEGRIN) and future directors of IRCM. (Mr Claude SARDET)

09h00 - 12h00 Closed-door coordination meeting of the Review Group with the DS (Dr Jean ROSENBAUM).

6 • Supervising bodies' general comments

Université Montpellier 1
AES Droit, Sc. politique Économie IPAG ISEM Médecine Odontologie Pharmacie STAPS

nouvelle université de Montpellier
un projet, une ambition

Montpellier, le 10 mars 2014

Monsieur Didier HOUSSIN
Président de l'AERES
Monsieur Pierre GLAUDES
Directeur de la section des unités
de recherche
Agence d'Evaluation de la Recherche et
del'Enseignement Supérieur (AERES)
20, rue Vivienne
75002 PARIS

Référence : A Pélegrin/C Sardet : S2PUR150008519-IRCM-Institut de Recherche en Cancérologie de Montpellier-0342321N

Messieurs,

Je tiens à remercier le comité de visite AERES pour la qualité de son rapport d'évaluation concernant l'Institut de Recherche en Cancérologie de Montpellier dirigé par Monsieur André PELEGRIN et pour le projet contrat quinquennal par Monsieur Claude SARDET.

J'ai bien noté les remarques du comité de visite et je veillerai à ce que celles-ci soient prises en compte par le directeur de cette structure de recherche.

Vous trouverez ci-joint les corrections factuelles et les observations générales formulées par le directeur et ses responsables d'équipes.

Je souhaite préciser que cet Institut constitue une structure de recherche majeure en cancérologie à laquelle l'Université apporte un soutien important comme en témoigne notamment la chaire mixte de professeur (Université Montpellier 1/INSERM) qui lui sera affectée cette année.

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

Philippe Augé
Président
De l'Université Montpellier 1

Directeur actuel :
Dr André Pèlegrin
Directeur Adjoint actuel :
Dr Charles Theillet
Porteur de Projet 2015-2019
Dr Claude Sardet

Montpellier le 5 Mars 2014

Response to the AERES report on IRCM and its teams

Institut de Recherche en Cancérologie de Montpellier (IRCM)
Inserm U896 - Université Montpellier1 - CRLC Val d'Aurelle (ICM)

Porteur de Projet 2015-2019: ***Dr Claude Sardet***

We thank the AERES review committee for both the time and work that it devoted to our achievements and projects. We thank them for their careful and in depth investigation of our strengths and weaknesses and for the excellent scientific interactions during the review last December.

Our reply is based on the weaknesses pointed out in the report and the related recommendations made by the committee. **Every team will briefly respond below for itself.**

André Pèlegrin
Directeur actuel

Claude Sardet
Porteur de Projet 2015-2019

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Comments concerning the Institute as a whole

We are very pleased by the positive evaluation of our collective accomplishments and projects. We appreciate that the review committee has perceived the efforts that have been made by our community to create, in a very short period of time (IRCM was officialy launched in 2008), a well organized and attractive Research Institute dedicated to Cancer in Montpellier. We will do our utmost to live up to the confidence placed in us by the committee and will now act to achieve our high-profile 2015-2019 objectives.

Minor comments

Due to the limited time devoted to the visit of our building during the review, the committee might have missed the following point:

- IRCM is hosted in **a single building with three T-shaped wings** built in 3 phases (1997, 2006 and 2013). During the construction of the third wing (opening november 2013), a particular attention was paid to the optimization of the communication between the different zones of the Institute. This led to the reorganization and relocation of several teams and support services (administration, laundry, conference room, tech. platforms). Of notice, we took care to mix senior and junior teams (Teams 7, 8 and 13) in the new wing.

Concerning common policies to ensure interactions among IRCM staff we would like to emphasize the following:

- Since the creation of IRCM in 2008, IRCM internal seminars are organized every Tuesday at 2 pm in English. All IRCM team members are attending and are asked to talk at this weekly event, including permanent and non-permanent researchers, clinician and scientists, PhD students and post-docs. It ensures fruitful exchanges between teams and favor internal collaborations. Once a year, PhD students are also organizing a one day meeting ("journée des étudiants en thèse de l'IRCM") where IRCM PhD students are asked to give a formal talk to IRCM staff in presence of a panel of external scientific personalities.
- The organization of an institute retreat, on a yearly basis and involving all IRCM staff, features high on our list of priorities for the next five years (2015-2019).

Comments made by the teams concerning their evaluation

Team 1 - Immunotargeting and Radiobiology in Oncology – *Mr André PÈLEGRIN*

We thank the committee for its evaluation and its positive comments. This short reply is based on the weaknesses pointed out in the report and the related recommendations made by the committee.

- The committee indicated that the biological test developed and now evaluated by our radiation oncologists to identify patients at risk of developing severe late fibrosis after radiation is “somehow at the fringe of the team’s main line of research”. As indicated also by the

committee, we are convinced that this test “is very important for the clinical practice” and will be useful in the future to select patients eligible to combination therapies. Concerning this latter point, the committee encouraged us to develop projects combining targeted therapies with radiotherapy. We are pleased to indicate that several projects along this line combining either anti-HER3 Mabs, anti-EGFR/HER3 mabs or regorafenib with radiotherapy have just been financed by our SIRIC.

- We agree with the committee that we have to reinforce our collaborations with molecular immunology teams. We are working to improve this point: i/ at IRCM with very fruitful collaborations with the new Team3 (several joint grant applications have already been submited since the recent inception of this team at IRCM); ii/ at the international level with the recent establishment of several collaborations, in particular, with German teams.
- We are aware of the risk of international competition on some mAb targets. This is why we conduct in parallel projects on validated targets and on novel and original targets that have been chosen according to a "niche" strategy. Concerning the recommendation to strengthen the CD71 project, we are pleased to emphasize that since the beginning of February 2014, a new PhD student joined our team to work on this project.

Team 2 - Functional screening and targeting in cancer – *Mr Pierre MARTINEAU*

The review committee is kindly warning us about the danger to become "only a collaborative technological team". In the past, we always took care to apply first our innovative technologies/methodologies to our own scientific questions; this to insure publication of our work with lab members as senior authors. We will continue to do so by combining MS imaging and intrabody-based functional screens to shed new lights on tumor resistance and its underlying mechanisms.

Team 3 - Immunity and Cancer – *Ms Nathalie BONNEFOY*

We totally agree with the AERES recommendations that are very positive for this new assembled team. We will pursue our efforts to narrow down our research themes on tumor microenvironment with a particular attention to both basic and applied aspects of our research projects.

Team 4 - Drug resistance and new cancer therapies - – *Ms Céline GONGORA*

We fully agree with the review committee’s recommendations to hire postdocs and to reinforce the bioinformatics aspect of our project. Of notice, we have hired two new postdoctoral fellows since the on site visit last December. Moreover, we have recently welcomed in the team a senior researcher with a permanent position who has good knowledge and relevant collaborations in the field of high throughput data analysis. This allowed us to initiate solid collaborations with biostatisticians and bioinformaticians.

Team 5 - Proteases, microenvironment and cancer – *Ms Emmanuelle LIAUDET-COOPMAN*

We agree with the review committee's recommendations to hire postdocs. Hence, since the on site visit of the committee, we have submitted grant and fellowship applications (pending) to hire post-doctoral fellows.
In addition, we are pleased to mention that a paper submitted at the time of the visit has now been accepted for publication in PNAS (Sebti et al.).

Team 6 - Signaling of Tumor Invasion – *Mr Peter COOPMAN*

We thank the committee for its evaluation and its recommendations. We would like to emphasize the following:

- Concerning the size and workforce of the group, two additional PhD students have joined the lab since the submission of the written report, making a total of three at present. Applications have been submitted for Post-doctoral fundings (pending).
- Concerning first/last author publications, please note that the group published 2 *Oncogene* papers and not 1 as mentioned in the report. We also published a paper in the *Int. J. Cancer* (IF > 6) that should be considered in the "*good cancer research journals*" published by our group. The collaborative papers were also published in good IF journals (*Cancer Res., Mol. Cell. Biol., J. Cell Sci., Cell Cycle,...*). Anyhow, the team is striving to increase the number and level of its publications via the merging of the two complementary groups and the recent recruitment of additional PhD students. Since the submission of the written report, 2 additional papers were published by the medical oncologist associated with our team, one research manuscript is under re-submission and two others are in preparation.
- The report mentions that "*there is a lack of participation of team members to national or international evaluation committees*". We take note of this comment but want to stress that team members have, however, been involved in national committees (INSERM CSS2 committee, 4 AERES visiting committees), in the ponctual evaluation of numerous grant applications for various french and foreign agencies, in national and international PhD thesis juries and in consulting for private companies.

Team 7 - **Epithelial cell proliferation and polarization** – *Mr Alexandre DJIANE*

We agree with the very positive comments of the AERES committee.

As a new team supported by the Avenir program, we acknowledge that at the time of the AERES visit the two CR1 senior scientists had not been working together. Since her arrival from a nearby CNRS Institute in January 2014, the new CR1 who joined our Avenir team has integrated very well within the group. She made sure that before joining the lab all projects she was working on in her previous lab were completed and is now working exclusively on the project and objectives of our team.

Regarding strengthening the integration of the team within IRCM/ICM, we are currently involved in

- creating Notch dependent HMEC models with team 10
- evaluating the incidence of MAGI complex mutations in prostate cancer with the department of radio-oncology at ICM
- developing synergies and common approaches with the head of the future Team 16 who has recently joined the IRCM and who has a strong interest and expertise in Notch signalling in mammalian Cancer (Cancer Cell 2012).

Team 8 - **Hormone signalling and Cancer** – *Mr Vincent CAVAILLES*

We thank the evaluation committee for the highly positive comments and appreciation on our activity and scientific project. We welcome the global appreciation of the committee highlighting that "*the team is performing very well on all grounds*". We obviously will take into account the only recommendation which is to avoid scientific dispersion. We would like to reassure the committee that we will keep in mind to stay focused on our strengths and know-how.

The AERES committee draws our attention on two potential weaknesses:

- First, although we had trained a lot of students during the past years, we have to hire new PhD students for the next 5-years contract. This is on the way and, since the AERES evaluation, we have already hired a PhD student funded by the Avempace III ERASMUS program and there are two other master students welcomed by the team who are willing to start their PhD in our laboratory in October 2014.
- The second weakness deals with the number of international collaborations. We accept this criticism and will do our best to improve our participation to international scientific networks. We have started recently a new collaboration with a laboratory at the University of Chicago for the conditional invalidation of the *Nrip1* gene in mice. Moreover, we are convinced that our paper (Lapierre et al.) very recently accepted for publication in the *Journal of Clinical Investigation* will improve our ability to establish such collaborations.

Team 9 - **Molecular basis of carcinogenesis** – *Mr Laurent LECAM*

We are thankful to the review committee for evaluating positively the research activity of our group.

However, we would like to point out a few mistakes that may have biased some minor aspects of the evaluation of our group, in particular regarding the scientific independence of our group and links to our current collaborator and future director of the institute, Dr. Sardet. Indeed, we would like to underline that although we have developed strong and fruitful scientific ties with Dr. Sardet's group over the past years as a logical follow up of some projects that were developed years ago in his laboratory, the independence of our projects remain total. Since we started the group in 2008 through the INSERM Avenir program, many other routes have been developed completely

independently of this collaboration, in close collaboration with internationally recognized research groups, including those headed by Pr. Jean-Christophe Marine (VIB, Belgium), Dr. Johan Swinnen (University of Leuven, Belgium) or Pr. L. Fajas (University of Lausanne). We obtained funding completely independently of the collaborative research projects developed with Dr. Sardet (ARC, Ligue contre le Cancer, INCa, Chercheurs d'avenir Languedoc Roussillon) that already represents 80% of our current budget and will further increase in size in the coming years. Those projects, in particular those aiming at characterizing the role of the p53 pathway in metabolism of normal stem and cancer cells, and its role during aging and transformation, have been started from scratch in IRCM and part of this work is now ready to submit for publication in major journals (including one major paper that we are currently formatting for Nature).

All other recommendations of the AERES committee will be implemented in the coming years (including networking for European funding), as planned even before the visit of the committee.

Team 10 – **Genetic and phenotypic plasticity of cancer** -*Charles THEILLET & Claude SARDET*

We wish to thank the review panel for its positive appreciation of our work and proposal. About the concerns raised by the reviewers we agree that our project, based on the reunion of small part (1/3) of C Sardet's current team at IGMM and that of C Theillet at IRCM, will face some challenges and are aware of them.

- The risk associated to the merger cannot be brushed aside. We can only say that we take this seriously and are working on it, organizing joint meetings and discussing projects. Dispersion is one among other risks that comes with groups comprising several senior researchers. Anyhow, we would like to emphasize again, this merger will correspond to a re-focusing of C. Sardet et al. on only a subset of their ongoing projects at IGMM, dealing with cell cycle safe-guards, checkpoints and metabolism, applied to models developed by C Theillet's IRCM team.
- Will the two PIs get along? Until now we can only say that we always had great pleasure interacting and working together. This started when both of us worked on the two SIRIC proposals, where we played instrumental roles, and was naturally prolonged when we put the new project for IRCM together. The project for our team was part of it.
- Concerning the apparent lack of PhD students, apart from the overall shortage of students that all BioMed labs in Montpellier are currently facing, we have taken steps in order to attract students in the new team. Mainly from abroad but also by being proactive in M2 teaching and by participating to the labex EpigenMed (Sardet).
- The limited number of international collaborations is a point we are currently taking steps to correct. Current C. Theillet's team has invested a great deal of efforts in the past 3 to 4 years building and characterizing original models (PDX and primary cell lines) and are now starting to capitalize on them. We feel that we are now in a position to undertake international collaborations on these models. Although this might not have been correctly indicated in our report, current Sardet's team at IGMM was and is still collaborating with foreign labs (Holland, Japan, Hong-Kong, Switzerland, Germany) and is participating to international networks (GDRI

France-Japan, Cancer Research).

Team 11 – **Fragile sites, checkpoints and cancer** - *Mr Arnaud COQUELLE*

As mentioned, the team was established in 2011 and is therefore still very young, which may explain most of the criticism raised by the committee. During this short period of time, we developed ambitious model systems with the objective of publishing our work in high impact factor journals, raised money until 2016 and increased the number of people composing the team.

- I agree with the review committee that the task force of the team (4-5 people) is not optimal yet, and that "the limited amount of persons implicated in the project is a severe restriction and that technical support was needed". However, to reinforce these aspects, we recently welcomed a high profile post-doctorant, who is asking for permanent position.
- The committee has some "*difficulties to delineate between the projects conducted by the team and other teams*" with which we collaborate. As clearly described in our grants - we would have been happy to answer to any question on that point - we feel instead that the work-packages of our projects are well identified and unequivocally assigned to our lab or to the different teams we collaborate with.
- We completely agree with the committee that we need to publish our results as soon as possible. My (PI) strategy is and has always been to try to publish my work in journals with high impact factor (in 15 years, publications in first or last author in Cell, Nature Cell Biology, Molecular Cell, EMBOJ, Cell death and differentiation…). The down side of this strategy, especially for a young team, is the time required for each publication, even if a lot of data are accumulating. However, we disagree with the fact that our "*project has so far produced no publications*": indeed, part of our results on the gate-keepers of genome instability has already been published in *Nature Cell Biology* (of notice, first and co-last author of this manuscript were from our lab) and in *Cell Cycle*. Moreover, we are in the final phase of writing of the second part of this ambitious project (focused on ATR) that required the development of original cellular models.
- Finally, the committee states that our projects are not "*well designed and focused*". As a matter of fact, these projects have been positively evaluated in the last years, by grant agencies such as INCa, ARC, ligue, FDF, or by other review committees, including the previous AERES committee, INSERM CSS or the Scientific Advisory Board (SAB) of IRCM. For example, the exact same team projects were positively evaluated during spring 2013 by the IRCM international SAB; with the following conclusion: *"The SAB considers that this is a well-focused project, timely and original. The PI has satisfactorily solved former caveats in its experimental system, like the reversion of mutations in the MSI context. Current projects are very promising, but publication of the work done during these past years is essential"*. In addition, we have secure funding, running up to 2016, to complete these projects.

Team 12 - DNA damage response - *Mr Bijan SOBHIAN*

We thank the committee for its evaluation. We would like to emphasize the following:

- The review committee states that *"The PI itself has published pioneering work **on transcription elongation** during his post-doc."* Of note, we want to stress out that the PI also contributed important work in the **DNA damage response** field as witnessed by well cited papers in major journals during his PhD: *Genes Dev*. 2006 (Co-first author, cited 115 times), *Science*. 2007 (First author, cited 288 times).
- The evaluation report also mentions that *"The project contains two parts, one with a clearly identified working plan dealing with the role in DNA damage response of a **known** protein, which is relocalized to the nucleus upon DNA damage induction"*. Our protein of interest is far to be known since it appears in a single pubmed paper. This protein is not only "*relocalized*" but also SQ site phosphorylated upon DNA damage.
- The report states that "*In a second part of his project, the PI proposes to identify all genes transcriptionnally modified upon DNA damage induction in order to find new players in the DNA damage reponse. **Since no specific focus is announced prior to undertaking this topic**, high is the risk that many options could emerge from the high number of genes fulfilling the criterion of being significantly up or down-regulated upon DNA damage. So, the rationale for the choice of candidates that will be finally characterized in depth has to be clarified from the beginning of the screen for building on a fully rationalized approach, and thus a project likely to reach (some of) its objectives*". As clearly stated in the project submitted to AERES: We will focus on regulation of cell cycle checkpoints through a short hairpin RNA (shRNA) mediated knock down screen. Interesting candidates will be further studied individually for their precise mechanism of action.
- The final conclusion of the review is: *"Altogether, the committee believes that the project still has to maturate and would strongly benefit from interacting with an expert in the DNA damage response."* We agree the project has to maturate since the team was evaluated 7 months after its official creation as an IRCM emerging team, and 3 months after the first postdoc joined the lab. As a matter of fact, the exact same project is supported by a very competitive startup grant from the FRM and has been favorably reviewed by several independent committees (Grant agencies (ARC, FRM), Inserm CR1 recruitment of the PI, IRCM SAB). Interaction with the scientific community is of course essential to advancement of science in general. As to the DNA damage response field in particular, we again want to stress out that the PI previously worked and published in a high-profile american lab working in this field; with whom he remains in close contact.

Team 13 - Epigenetic, cell Differentiation and Cancer - *Ms Florence CAMMAS*

We thank the AERES review committee for its careful and in depth investigation of our scientific activity and project, and we fully agree with its recommendations. However, We would like to emphasize the following:

- It is stated that our team was established in 2011, however the official starting was in November 2011. Furthermore, several events have further delayed the real start of the team, i/ delay in transfering grants and animals (March 2012) from IGBMC (Strasbourg) to IRCM, ii/ delay in recruiting the first post-doc (April 2012), iii/ delay due to a contamination of IRCM animal facility.
- It is now widely accepted that cancers in general, and HCC in particular, are characterized by chromatin structure alterations. Therefore, we believe that the *in vivo* study of proteins that are at the cross-roads of multiple chromatin associated functions, such as the HP1s, is bound to lead to major findings of general interest in cancer biology. However, we are aware that the relevance of our findings on HP1 proteins (HP1 KO animals develop liver cancers) to human liver cancers remains to be formally established.
- We are also aware that we still have a lot to learn about liver physiopathology. Therefore, we have recently initiated several new collaborations with experts in the field and are attending specialized meetings on this topic. Soon, we will also submit a project to the French Hepatology network to obtain biopsies and cell lines of interest. This will certainly help to better understand the puzzling functions of the HP1 proteins within human liver, as unexpectedly revealed by our animal models.

Team 14 - Biology of Lysine Methylation and Cancer - *Mr Eric JULIEN*

We thank the review committee for the highly positive appreciation on our scientific project.

The report states that *"the main weak point is the lack of PhDs, post-docs and technicians »*. Since the onsite visit, we have recruited a new post-doctoral fellow on our funding and are in the process of selecting a second one that will be sponsored for fellowship applications to cancer research agencies. Our team has also recently recruited a new PhD student (2013, Ligue Contre le Cancer) and is welcoming a Master2 student who wishes to join us for a PhD next September.

Team 15 - Integrative cancer research for personalized medicine in digestive oncology - *Mr Marc YCHOU*

We fully agree with the positive comments and recommendations made by the review committee. Few remarks concerning the weaknesses and threats.

- The report states that « *The members of this new team have to learn to work together* ». As a new team, we can only agree with this comment, however, we want to stress out that in the past several team members have already been successful in designing, implementing, and

publishing together, including studies issued from close collaborations between clinicians and researchers.

- It is also stated that « *The team has now to be internationally recognized as a whole* ». We fully agree and add this is one of the main driving objective that led us to propose the creation of this team.
- There is also a concern about the *"Low percentage of researchers at the bench to increase basic research in synergy with the other IRCM teams* . We believe instead that the team as proposed will be able to fulfill this objective. Indeed, the team includes 3 full time senior researchers with permanent position from CNRS/INSERM. Moreover, we have secured funds to recruite post-docs and PhD students in 2014, and have already launched calls to identify them. We expect that by the creation of the team next January 1st 2015, 1 postdoc and 4 additional PhD students will have joined us. In addition, as it is carried out now, our projects already beneficiate from collaborations with several other IRCM teams.
- Concerning the « *Multiplicity of research topics* », please note this is the current situation, i.e. before the creation of the team (January 2015). As mentioned in our report, our complementary expertise will first serve a common and new project aiming at exploring resectable liver metastases from colorectal cancer, from the description of their molecular and cellular phenotype and origins, to their detection, diagnostic and treatment by innovative approaches.
- Another comment states the « *spatial spreading of team members*". The creation of the team will permit to cluster its members into a single lab space at IRCM which is directly connected with the Cancer Hospital ICM.