IRCM - Institut de recherche en cancérologie de Montpellier

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Institut de Recherche en Cancérologie de Montpellier

From the

University Montpellier 1

INSERM

CRLC Val d'Aurelle

May 2010

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Le Président de l'AERES	Section des unités de recherche
	Le Directeur
Jean-François Dhainaut	**Pierre Glorieux**

May 2010

Research Unit

Name of the research unit : Institut de Recherche en Cancérologie de Montpellier

Requested label: UMR_S INSERM

N° in the case of renewal: U896

Name of the director: Mr. André PELEGRIN

Members of the review committee

Chairperson :

Mr. Olivier DELATTRE, Institut Curie, Paris

Other committee members

Mr. Jorge S REIS-FILHO, The Breakthrough Breast Cancer Research Centre, London, UK

Mr. Hinrich GRONEMEYER, Université de Strasbourg, Illkirch

Mr. Mef NILBERT, Lund University, Sweden

Mr. Hervé WATIER, Université de Tours

Mr. Jean-Luc TEILLAUD, Centre de recherche des Cordeliers, Paris

Mr. Enrique de ALAVA, IBMCC, Universidad de Salamanca-CSIC, Salamanca, Spain

Mrs. Catherine-Laure TOMASETTO, Université de Strasbourg, Illkirch

Committee members nomminated by staff evaluation committees (CNU, CoNRS, INSERM and INRA CSS....)

Mrs. Sophie BROUARD, Nantes, INSERM CSS member

Mrs. Christine PERRET-MAYEUX, Paris, INSERM CSS member

Mr. François GUILLEMIN, Université Nancy 1, CNU member

Observers

AERES scientific advisor

Mrs Marie Annick BUENDIA

University or School representatives

Mr Jacques MERCIER, Vice-president, Université Montpellier 1

Mr Jean Bernard DUBOIS, Directeur Général du Centre anti-cancéreux de Val d'Aurelle

Mr Marc YCHOU, Centre anti-cancéreux de Val d'Aurelle, conseiller médical

Research Organization representatives

Mrs Viviane LEBOURQ, ADR Inserm Languedoc Roussillon

Mrs Chantal LASSERRE, Insem CCS2

Report

1 • Introduction

The site visit took place on December 16th and 17th 2009. After a general presentation of the organization and scientific strategy of the Unit by the head of the laboratory, the committee met with representatives of the University, of the INSERM and with the Director of the Val d'Aurelle Centre. Each of the seven team leaders then presented their projects in 45 minutes followed by 15 minutes of discussion. The committee was then split into three parts to meet i) Ph.D. students and post-doc, ii) engineers, technicians and administrative assistants, and iii) researchers with permanent position. At the end of the visit, the committee had a closed-door meeting to prepare the report.

IRCM is located in the Val d'Aurelle Centre de Lutte contre le Cancer campus in Montpellier. Around 140 people are working at IRCM including 28 permanent scientists. IRCM started in 2007 with six groups. By the end of 2010, the group Metabolism and Cancer will move to the campus of IGMM to join a task force on metabolism. Reciprocally, two new groups were created: one "Molecular basis of carcinogenesis" is headed by a team leader who was awarded an INSERM AVENIR grant. The other one is "Cathepsins, autophagy and cancer" headed by a team leader who was recently given an emerging group status within the IRCM.

The research field of IRCM on cancer is rather broad, with three main research orientations: i) nuclear receptors and hormone dependent cancers, ii) genetic profiling and iii) therapeutic antibodies/radioimmunotherapy.

IRCM is headed by a director assisted by a deputy director and by a general secretary. All important decisions are taken by the board of team leaders. Considering budget and fund allocation, core budgets from INSERM and University are mainly used for common running costs. A portion (30%) of this core budget is nevertheless distributed between the teams taking into account a coefficient which is dependent upon the ranking of the group after evaluation. The different groups are also active to apply to various funding agencies. Part (20%) of the research contracts are allocated to the common budget. It is also important to note that the IRCM has set up an international scientific advisory committee composed of prominent scientists who can advise the director of the IRCM on different aspects including strategy and recruitment. Unfortunately, the recommendations made by this committee were not available to the AERES visiting committee.

- Production results

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	8	8
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	25	22
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	21	18
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	14	11
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	18	13
N6: Number of Ph.D. students (Form 2.7 of the application file)	23	15
N7: Number of staff members with a HDR or a similar grade	26	26

2 • Overall appreciation on the research unit

It first has to be stated that, due to phasing with the University, the IRCM is evaluated only two years after it was created. The IRCM proposes to establish a strong potential in cancer research within a clinical cancer centre with the aim to create a comprehensive cancer centre as they exist in the US. This project fits with the strategies developed by the different administrative partners including the Val d'Aurelle Cancer Centre, the Inserm and the Montpellier University. The different teams are mastering a number of technical approaches and cutting edge technologies. Technological facilities of very high level are available in the Montpellier area or developed in house. The main IRCM scientific orientations are based on expertises of the founding groups in nuclear hormones, genomic profiling and therapeutic antibodies. Important achievements have been made in the past few years and have led to good publications and patents and to the spin-off of three biotech projects. Yet, the proposed orientations are still very broad for a middle size research centre and the number of separate projects is quite large. This decreases the overall visibility of the research that is conducted in some of the teams. The departure of a strong group and of additional scientists is both challenge and chance to the Institute. Together with the future expansion of the campus it permits the recruitment of new group leaders based on competitive calls that consider the need to focus strength on a limited number of research axes. Internal, transparent and competitive promotion should also lead to uphold ambition and motivation of talented young scientists. Three main challenges are ahead the Unit. One is to deepen and strengthen the connections between the research conducted in IRCM and the clinics of the Val d'Aurelle centre. Indeed, this connectivity is one of the important strengths of the IRCM which should be developed further. A second one is to develop an in house bioinformatic platform which is critical to all future developments dealing with large scale data analyses produced by the modern global technologies. Finally, a key point is the recruitment of talented young scientists.

- Strengths and opportunities

- IRCM is located in the vicinity of very active research institutes. The integration of IRCM in the Montpellier campus is excellent and dialogue between the different Institutes of the Montpellier area enables non overlapping, highly competitive facilities to be developed and made accessible easily. In that regard, the IRCM is developing a very promising animal histology platform.

- IRCM benefits of strong supports from the Cancer Centre since the salaries of many staff people are funded by Val d'Aurelle.

- The Val d'Aurelle campus will expand. A new building should open in 2011, hence enabling the IRCM to plan the recruitment of new teams.

- The location of IRCM within a Cancer Centre is a strong asset to connect basic research and clinics and a very strong opportunity to develop clinically relevant projects. In this respect the identification of a medical adviser whose role is to facilitate such collaborations is a very good initiative.

- IRCM has recently proven its ability to recruit talented young scientists.

- Having lab meetings in English is an important step toward internationalization of the Institute

But weaknesses and threats also have to be pointed out :

- The number of separate projects IRCM is running is too high, with an overall impression that the unit is made of a collection of heterogeneous projects that develop independently, even within groups.

- Plans to develop new genomic technologies are lacking (in particular for next generation sequencing). The lack of bioinformatics may constitute a considerable handicap for future global studies.

- It is not absolutely clear how much the IRCM scientific strategy is discussed and coordinated in relationship with the strategic plan of the Val d'Aurelle Centre. Apart from a few projects, the real links with the hospital are still scarce; in particular the connection with the pathology department of the hospital, a crucial link for all cancer-related projects, could be more developed. Similarly, there seems to be a lack of strong connection with a routine molecular biology lab within IRCM or at the regional level.

- The unit appears too self-centred. The opening to the regional, and even more importantly, to the national and international scientific communities can certainly be improved.

- The limited funding from international funding agencies is a serious issue that need to be addressed.

This leads to propose some recommendations to the head of the research unit

- To increase focus and to define research priorities and plans for future developments. To limit the number of separate projects within each team by at least 2 folds. Focusing on a smaller number of topics will help to reach more visibility and higher impact of publications that originate from the IRCM teams.

- To have a better integration of the different projects within each team and to provide incentives for collaborations within and between teams

- To strengthen the external communication of the Institute, in particular through an updated and complete English version of the web site and through more participations to international meetings.

- To attract young scientists through competitive international calls.

- To define a clear process for the internal promotion of new team leaders.

- To strengthen the links with clinicians of the Val d'Aurelle cancer centre, in particular with the pathology department and with local or regional routine molecular pathology labs.

- To open the IRCM to the regional, national and international scientific communities.

- To recruit at least one bioinformatician. Being connected with bioinformatic labs or platforms in Montpellier or elsewhere is important but given the evolution of profiling technologies it is mandatory to have in house expertise.

- To strengthen in house pathology support

- To participate in the steering committee of the Val d'Aurelle centre

- Data on the work produced:

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	35
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	6
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)] x 100	35/36
A4: Number of HDR granted during the past 4 years	7
A5: Number of PhD granted during the past 4 years	26

This table shows that almost all scientists of the IRCM can be considered as active in research. Nevertheless there are strong variations. Most researchers have a good and regular scientific production. For others the production is more sporadic, concerns secondary coauthorships or relies mostly on reviews rather than on original publications.

3 • Specific comments on the research unit

- Appreciation on the results

The relevance of the research conducted in the IRCM regarding cancer research is high. All groups have this focus. Some important achievements have to be highlighted: 10 patents have been deposited and 3 are published; 3 biotech projects have been generated (AbChem, SurgiMAB and NanoMedSyn); 3 clinical trials directly resulting from IRCM projects (LIBER, late toxicities after radiotherapy and THERAPY projects).The IRCM should be congratulated for very concrete results in term of patent depositions and development of biotech companies.

The publication record of the IRCM is generally good. All groups have publications in good or very good specialist journals. However, most publications in top journals have been made either by the group « Metabolism and cancer » that recently left the institute or in former labs of scientists who recently joined the institute. On the one hand it is very reassuring that the Institute has the attractiveness for bright scientists. On the other hand, it also indicates that presently the Institute has too few publications in high level, multidisciplinary journals, originating from work primarily carried out by members of the IRCM. Given that the relative number and quality of publications per permanent scientist is yet to achieve an optimal level, it is not surprising that the number of participations of IRCM scientists to congress or meetings as invited speakers is still relatively low.

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

The number of students or post-docs from abroad is suboptimal. Most groups mention the difficulties to find and finance PhDs or post docs pointing out the need for an overall strategy, possibly in collaboration with the University, aimed to recruit students and post docs. In that respect, it is certainly important to concentrate efforts towards the external communication of the Institute, locally and internationally, to more efficiently attract Ph.D. students or post docs. Presently, most of the web site is written in French and some parts, including the PhD and post doc sections are blank. Importantly, the IRCM has recently been able to attract very talented young scientists and it should therefore be very much supported to pursue in this direction. The vicinity of the hospital, the lab space, the facilities and expertises of the Montpellier area as well as continuous support from the Cancer Centre constitute strong assets.

In addition to strong support from INSERM and the Cancer Centre, the different teams of the Unit have proven efficient in getting competitive funding from the ANR, the INCA and through the industry. Some efforts should certainly be made towards European funding agencies. The participation to international or national scientific networks and the existence of stable collaborations with foreign partners should be prioritized.

- Appreciation on the strategy, governance and life of the research unit

The director of the IRCM appears to be well appreciated and respected by his colleagues. Important decisions involve the board of group leaders. Young scientists could certainly be advantageously and officially associated with important decisions. Although the nomination of a medical advisor facilitates the communication between the research unit and the hospital, it appears that important efforts still have to be made in this direction and that the number of projects involving both scientists and clinicians from the Val d'Aurelle centre is still relatively low. The link to the experimental/biological part of the clinical studies could be strengthened also through attracting the analysis of biological factors within some of the many clinical trials. Biomarker skills in the clinical trial setting could indeed represent a niche that links the clinic to the labs. In this context, the creation of mixed clinical-research positions in order to get the doctors into the labs, as Inserm interface grants for clinicians, could be proposed.

- Appreciation on the project

It is important to note that the Unit has been able to provide emergence for a new group headed by a former member of the "hormone-dependent cancer progression" group. Similar initiatives should be encouraged since most of the groups are quite large, with a significant number of scientists with permanent positions, some of them having a very good track of records. Encouragements and incentives for the emergence of cutting edge projects and taking of risks leading to progressive autonomy are certainly important to motivate the young scientists of IRCM and particularly those who joined recently. It may be conceivable that the call for proposal to host new research groups may also enable inside scientists to apply in a competitive manner.

The director together with the board of team leaders is encouraged to define clear priorities for the Centre for the next years and reduce the number of projects. Some projects are historical and their relevance to the present project of the Institute should be re-evaluated. The priorities of the IRCM should also be defined taking into account the overall medical and scientific strategy of the Val d'Aurelle Centre.

4 • Appreciation team by team and/or project by project

Team E1 : Hormone signalling and cancer

Team leader: Mr Vincent CAVAILLES

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	3	3
N6: Number of Ph.D. students (Form 2.7 of the application file)	5	3
N7: Number of staff members with a HDR or a similar grade	4	3

- Appreciation on the results

This group focused on hormone dependent breast cancer and on nuclear receptors, including oestrogen receptor and androgen receptor. The research portfolio was extensive and divided into three main areas: i) characterisation of synthetic and environmental NR ligands, ii) oestrogen receptors and hormone signalling and iii) role and mechanism of action of NR coregulators. The latter comprised a loose collection of multiple approaches and projects.

A total of 21 original manuscripts primarily arising from the group were published from 2004 to 2009, including only 4 papers in journals with impact factors higher than 5. Hence, although this group is consistently contributing to the field of nuclear receptors, the contributions are mostly confirmatory and incremental. Proffered papers and posters were only presented at National or European conferences and meetings, which may limit the recognition of the group internationally.

There were numerous collaborative efforts that have led to some high impact publications; however these were not directly related to the focus of the group. Results also include four licenses with pharmas.

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

The group leader was awarded the Grand Prix Ruban Rose de la Recherche in 2009 which indicates a strong national recognition. Concerning international links, of note is the collaboration, which stems from the training of the group leader, with a recognized team in UK. Of note are also the participation to the Réseau Européen Cascade and the collaborative effort with a team at the University of Granada. However international recognition seems not to be completely within reach at this stage with permanent scientists of the group being invited to a relatively limited number of international lectures, none of which in North America.

The transcriptional modulator screen has proven to be a useful platform to attract over 1M Euros funding from pharma companies. Four cell lines have been licensed to pharmas. It should be noted, however, that it is unclear whether the industry-sponsored projects have been used for 'contract research' or to further develop the aims set out by the group leader.

- Appreciation on the strategy, governance and life of the research unit

The projects currently being developed in the group are organised around the theme of nuclear receptors signaling. However, it is not really easy to see the overall coherence between the multiple scientific projects, the development and use of the screening platform and the collaborations of the group in clinical trials. The precise role and responsibility of each permanent scientist in the different projects could advantageously be clarified.

The head of the group is involved in teaching activities in the 'Doctoral School of Biology and Health' at the University of Montpellier I and II. Connections with the Val d'Aurelle Centre have been established and clinical research fellows have been incorporated in the group.

All scientific investigators have their diplomas for Research Training (HDR).

- Appreciation on the project

The project is ambitious and covers three broad and very competitive topics, namely 1) Characterisation of NR ligands and transcriptional talks with ERs, 2) Role of oestrogen receptors in hormone-dependent cancers and 3) Study of ER transcription coregulators. Each of these main topics is divided into a series of projects, with an overall visibility which is suboptimal. A substantial proportion of the proposed work is centred around RIP140, first characterised by the head of the group as a transcriptional modulator of ER back in 1995, whilst he was still working in his post doc's lab. Loss and gain-of-function mouse models for RIP140 that are planned should include conditional systems. The study of the possible involvement of transcription co regulators (ex HDAC9) in breast cancer, could benefit from a broader analysis of their expression and structure, taking advantage of published or in house (generated from other groups in the unit) microarray data.

There is the concern that the group may be over-stretched with the number of projects proposed and the resources available. It was felt that the proposed approaches somehow neither address the questions on a global level nor are focused enough to provide a sufficiently deep analysis to allow the group to be optimally competitive on an international level. A clear strategy to determine which projects should be terminated or prioritised is of utmost importance for the success of the group.

- Conclusion

This research group has substantial experience and consistent scientific output in the field of nuclear receptors and transcriptional modulators without, to date, paradigm shifting contributions. The transcriptional modulator screen platform has proven instrumental to set up collaborations with industry and to attract pharma funding; however, a clear strategy to use this funding to address questions either in a global fashion or in greater depth is yet to be defined. Although of interest, the clinical trials being carried out are not all directly related to the main scientific questions posed by the group.

The main strengths of the group are i) the transcriptional modulator screen platform; ii) the initiated collaborative efforts with the hospital; iii) the ability to attract funding from pharma; iv) the multidisciplinary nature of the group.

The weaknesses are i) the very diverse nature of the projects being proposed; ii) the limited novelty of the projects and of risk taking initiatives; iii) the lack of focus in addressing the scientific questions; iv) the difficulties in generating data of sufficient depth and breadth to lead to high impact publications; v) the still limited collaborations with international leaders in the field of nuclear receptors; vi) the collaborations with the hospital and clinics that are not directly related to the main scientific aims.

Some recommendations can therefore be made:

- To consider addressing the scientific questions in a global (i.e. genome-wide, epigenome-wide or proteome-wide) fashion.

- To increase participation to international or national scientific networks, to establish stable collaborations with foreign partners, particularly in the field of nuclear receptors and transcriptional modulators. This may also help to attract bright young researchers from abroad.

- To define a clear strategy to maximise the impact of the industry-sponsored initiatives on the group's research portfolio. In particular, a clear perspective for the future of the modulator screen platform should be developed. This could be done, for example, by defining novel ligand binding modes followed by an in depth structural-functional analysis, developing tissue/cell type-specific reporting systems, modulating coregulator content, etc., or use it as a plain service. The group would benefit from having a clear policy about the types of industry-sponsored research should be considered as 'service provision' or as primary research endeavours.

- To define a strategy for the prioritisation of some of the projects, the termination of others and for the integration of the distinct scientific questions being posed.

- To revisit some of the aspects of the proposed work (e.g. the proposed mouse models; the involvement of transcription co regulators in breast cancer).

Team E2 : CELL SIGNALLING AND CANCER

Team leader: Mrs Dany CHALBOS

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	7	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	4	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	1
N7: Number of staff members with a HDR or a similar grade	5	2

- Appreciation on the results

In its past format, this large group was oriented toward the molecular characterization of hormone-dependent breast cancer progression with research themes covering a variety of areas fom clinical to fundamental studies. The relevance of the research was high given the prevalence of hormone-dependent breast cancer. Some of the themes were quite original, including the study of a novel mechanism of action for Cathepsin D and the revisited use of Mannose 6-phosphate for targeted therapies.

The number of publications that were produced is average regarding the size of the group. Two papers were published in high impact journals (Nat Cell Biol; Mol Cell Biol) and the bulk of the publications were in good specialized journals. The PTPL1 project has been reasonably productive with publication in Cancer Research, International Journal of Cancer and International Journal of Biochemistry Cell Biology. Considering the Fra-1 project, the last publication (Oncogene) was in 2005. Most publications do not associate different PIs from the group underlying a certain lack of connection between the different themes that are developed in the group. Five patents were deposited but no licensing has been reported to date. It is of note that a large part of the production and most of the patents obtained were on the behalf of a PI who is leaving the group. Regarding the size of the group and the presence of many PIs with HDR, only 4 PhD theses were defended in the past quadrennial.

- Appreciation of attractiveness

The different PIs have national and international collaborations with common funding and/or collaborative publications in good journals (MCB, JBC, JCS). There is little collaboration with the other groups of the centre. The local and national visibility is clear with several invitations and organization of conferences. The international visibility is relatively modest, with few mentioned invitations for lectures or international meetings. The Dendrimont-Benicourt price from the Institut de France was awarded to the head of the group.

The group recently recruited a talented young scientist on a permanent position and mentorship was successful since one of the former young PIs is now developing her own group in the institute. The number of students is relatively low, and there are no foreign student or post-doc. Of note, one of the senior and productive PIs is leaving to create a new team in a different institute. Several competitive grants (EU-, ANR, INCA …) have been obtained.

- Appreciation on the projet

Being recently reorganized with the departure of two PIs, the group has changed its main interest towards cell signalling and cancer. Its main focus is related to triple negative breast cancers, a very relevant issue in breast cancer research. However, to date, the project appears to be rather aimed at the molecular characterization of sets of genes or pathways of potential interest in breast cancers without obvious specificity to triple negative cases. This molecular characterization includes mainly Fra-1, PTPL1, SRC/beta-integrin signaling, beta-catenin signaling. Though some preliminary results from the group suggest that these genes or pathways may be involved in cancer, more data need to be generated to be fully convincing of their real involvement in breast cancer and to more precisely define in which subtype of breast cancer. The location of this group within a Cancer Centre with easy access to tumour material should considerably facilitate such investigation.

The project as described is mid-term and based on candidate gene or pathway –driven hypotheses. The methods proposed are classical and well established in the laboratory and should provide interesting results. However unbiased, large scale methods to study the function of novel genes, especially transcription factors, should at least be considered for a long term project.

- Conclusion

The group has been destabilized by the departure of two permanent scientists and is emerging in a new, smaller format; it is composed of 2 experienced PIs and of one recently recruited junior scientist. The head of the group has a relatively low number of recent publications as a senior author. By and large the overall visibility of the group is weak and the new organization that is proposed does not appear as mature yet.

The project aims at the molecular characterization of genes or pathways possibly involved in breast cancer progression. Relatively low risk approaches in the continuity of the previous research are chosen and hence lead to the feeling that the project lacks ambition. Although methodological links exist between the different themes, at the scientific level the connections appear somehow artificial. How this may mature in the future is unclear. In those circumstances, a particularly strong leadership would be required to engage the group into modern technologies and more risk-taking hypothesis. This would also be critical to prioritize and connect the themes.

The strengths of the group are the robust expertises in signal transduction analysis, the recruitment of a young scientist after a productive post-doc abroad and the potential access to clinical samples.

The weaknesses are the scientific focus, the overall organisation of the group and its leadership that have to be discussed in depth to define a clear strategy for the next four years.

As recommendations, the group should

- Revisit and hence possibly strengthen his focus on triple negative breast cancers. Provide convincing evidences that the various projects are relevant in this very competitive field. In house connections should be increased, especially to validate that the selected genes are important in breast cancer and more precisely in triple negative breast cancer. Links with clinicians involved in the management of triple negative cases should also be reinforced.

- Prioritize some projects and possibly terminate others. A priority should be given to the themes that are validated and connected together.

- Establish national and international collaborations on the field of triple negative breast cancer if this is the main focus to be pursued. Increase participation to international or national scientific networks.

- Consider using unbiased, high throughput technologies.

Team E3: CATHEPSINS, AUTOPHAGY AND CANCER

Team leader: Mrs Emmanuelle LIAUDET-COOPMAN

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	3
N7: Number of staff members with a HDR or a similar grade	1	2

- Appreciation on the results

This team is emerging from the previous « Control of hormono-dependent cancer progression » team.

The group has shown that cath-D secreted by cancer cells plays a key role in tumour microenvironment. In particular it may degrade CystC which is a cysteine protease inhibitor and interact with fibroblasts through a cell surface receptor that may be LRP1. AItogether they show that the role of CathD may rely on protease dependent or independent mechanisms of action.

Nine original papers have been produced over the 2005-2009 period by the two researchers of this team; very interesting ones have been published almost 4 years ago (J. Cell Biol., Cell), on cathepsin and on autophagy. The number of publications of the PI as a senior author is still relatively low (3), the last one being from 2006. Of note, two manuscripts are in preparation.

An international patent has been deposited in 2009. No licensing/commercial exploitation agreement has been signed so far.

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

The number of invited lectures/international conferences is still modest which is a quite an expected situation for an emerging group with rather young scientists.Two seminars outside France have been given (Luxembourg, Sweden) ; 7 seminars have been given in France. Posters have been presented including 2 at Keystone Symposia (2005, 2008), 2 at AACR (USA) (2005), 1 at an EMBO workshop (Italy) (2005) and 1 at the 14th Euroconference on Apoptosis (Italy) (2006).

One Thesis has been successfully achieved in the 2004-2007 period.

The number of good quality partnerships is intermediate. Collaborations are mainly with groups involved in fundamental research, except for the work performed with the French biotech company Hybrigenics (identification of Scythe as a new partner of cath-D). Partnerships rely on previous training labs and on participation to one EU-funded project. The group has interesting ongoing collaborations with various teams from the Montpellier area but also from France, Europe or Canada. A recent paper was published within the frame of the FP6-funded network on mechanisms of chemotherapy resistance (Int. J. Cancer, 2009).

The group does not host foreign students or post docs. Importantly, a scientist with excellent recent papers on autophagy was attracted to the group in January 2009, following a previous scientific partnership. Excellent synergies exist between this particular researcher and the PI.

Some competitive funding has been obtained, although in a moderate amount (<20.000 €/person x year). Several projects are being funded until the end of 2009. Only one project (EU-funded) will be active in 2010. It is hence important for the team to successfully raise new funding in 2010.

No teaching activity is indicated in the written document, but the team is very active at the local level by organizing internal seminars and lab meetings.

- Appreciation on the project

This is an example of a bedside-to-bench approach. The characterization of the action mechanisms of a prognostic marker in breast cancer (cathepsin D) is of strong interest for developing medical applications based on the manipulation/targeting of this molecule in oncology. Studies on both Cath-D receptors and Cath-D substrates as well as on their role in regulating gene transcription are fully relevant and well-adapted to a Cancer centre environment. The group has developed an ambitious but feasible research program on the molecular mechanisms of cathepsin-D function, especially on LRP1, which was shown to be the fibroblastic receptor of cathepsin-D. As a therapeutic approach, the group also obviously decided to work on reagents blocking the interaction between cathepsin D and target molecules. Original parts of the research project (both in terms of novelty and invention) are the study on cath-D role in the nucleus and the study on the role of the LRP1 (a receptor of Cath-D) in autophagy of cancer cells. These projects are clearly risky but should benefit from the complementary expertises in Cath-D and autophagy of the two scientists with permanent positions. The overall hypotheses are promising for an emerging group both in quality and impact.

- Conclusion

In conclusion, this is a promising emerging group, in which the PI shows a strong commitment with her group and her career. The scientific project for the mid-term is very good, with translational interest and convincing feasibility based on state-of-the-art technical and scientific skills. There is clearly some risk taking, in particular for the project on the role of cath-D in the regulation of gene expression based on its nuclear localization.

The group has good potential to attract young talented researchers and is placed in a good environment which will be helpful for its growth. In fact, making this team autonomous certainly represents a true « plus » for the IRCM, based on the dynamism and talent of the two founding young researchers.

The main threats are the under financing of the group in the long term, and the relative lack of relationship with the clinical groups working in breast cancer and with the industry, since the results and projects of the group have a strong translational potential.

Hence, the PI should strengthen the relationships to other groups (national or international) working on extracellular proteases, as well as with the main regional or national breast cancer clinical groups and should develop a plan to translate the results to the clinical field. Also, this small emerging team should remain focused on the most original proposed subjects of their research plan

Team E4: Molecular basis of carcinogenesis

Team leader: Mr Laurent LE CAM

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	3 to be recruited
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	2	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	2
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

Understanding the mechanism involved in physiological self-renewal and altered in tumorigenesis is of critical importance in the cancer field. The project aiming to understand the role of E4F1, a transcription factor for which the team leader discovered an ubiquitin ligase activity against p53 during his training at IGMM, (Montpellier), is original. This result was published by the group leader as first author in Cell in 2006. The function of E4F1 in stem cell homeostasis, aging and tumorigenesis is now addressed using several genetically modified mouse models developed by the team.

The yet unpublished results obtained by this young team, recently installed at IRCM, are very convincing and should bring outstanding contributions with high impact. A manuscript is currently submitted to Genes&Dev.

The publication record does not yet relies on the own data of the team obtained at IRCM, which is not surprising given the recent installation of the team and the length of experiments based on mouse genetic. The 2004-2009 publication record includes Cell in first position in 2006 and co authorships in Oncogene and Nat Cell Biol.

- Appreciation on the attractiveness

The team leader is a young scientist who was granted with an "INSERM Avenir" grant in 2008 which constitutes a good label for attractiveness. Together with the team leader, the group includes one permanent position researcher (CR), two PhD students, two engineers and two post-doc that will be recruited next year. The funding raised by the leader is at the beginning and should be sufficient to perform the current research program. It seems to guaranty the success of future applications.

- Appreciation on the strategy, governance and life of the group

The team appears to be excellent in terms of strategy and management. The team leader has set up many national (including co-shared thesis with former post doc lab) and international collaborations with groups working on chromatin remodeling, genetic screeing and proteomics to perform the proposed research.

The development by the team leader of a very efficient histology core facility able to deliver virtual sections that could be analyzed at distance by pathologists is remarkable and should be congratulated.

- Appreciation on the project

The project is a follow-up of the current achievements. The main topics that will be developed are centred on the epidermis and hematopoietic compartments. The role of E4F1 in epidermal and hematopoietic stem cell homeostasis will be addressed by using a variety of genetically modified mice with constitutive or conditional E4F1 gain- or loss-of-function mutations and by cell transplantation experiments. The genetic, cell biology and biochemical angles of the project appear very convincing and promising. With respect to oncogenesis, the observations showing that E4F1 is involved in the p53-dependent control of senescence and may be an essential survival factor of transformed cells are of outstanding interest. All the genetic tools and expertise required to perform the work are present in the team.

- Conclusion

This young team is promising and dynamic and has developed original resources to perform projects that should be successful.

Given the critical importance of mice experiments and in particular the numerous crosses that are required, a potential threat may concern the limitations of the capacity of the IRCM animal facility.

Collaborations with other groups are encouraged to set up the integration of this young team at IRCM. It is also certainly important that the team remains focused on the very interesting observations that were made recently and concentrate on rapid publication of the results. It is of upmost importance that the group rapidly attract talented post docs.

Team E5: Tumor Identity and Plasticity

Team leader: Mr Charles THEILLET

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	7	4
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	4
N7: Number of staff members with a HDR or a similar grade	3	4

- Appreciation on the results

This research group has developed three different projects. One was aimed at the understanding of the mechanisms that govern chromosomal breakage in cancer. One investigated the differentiation pathways in breast cancers and the last one focused on genetic profiling of breast cancer.

Altogether the group has published or is associated with 16 publications from 2005 to 2009.

The two first projects led to excellent publications in Nat Cell Biol (2009), highlighting the role of toposomerase I in genome stability, and Mol Cell Biol (2008), on the role of Erk5 on keratinocyte activation during wound healing. The two PIs responsible for the first two projects were senior authors of these manuscripts. The scientific production of the last project has been lower with mainly two publications with senior authorship in Oncogene on the comparison between ductal and luminal breast cancers and in British Journal of Cancer on the genetic profiling of genes on the long arm of chromosome 1.

The remaining publications were done in collaboration and published in good specialized journals.

The research profile and scientific output of the group is perceived as relevant and of high quality. The quality and stability of research partnerships, including national and international collaborations/consortia, is perceived as good with collaborative manuscripts with groups in Lyon, Marseille, Belgium, Norway and at the NCI.

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

No record was provided as regards to prize or other distinction. Regarding recruitment of top-level scientists, the research group mainly consists of French researchers, which suggests potential for increased international recruitment. There is one clinical oncologist in the group, although his role is not explained in depth.

The group has demonstrated good abilities in fund raising with successful applications for competetive funding. No records are provided regarding participation in industrial relationships/clusters or references to patents.

The group has a leading role in the breast Carte d'Identité des Tumeurs programme of the Ligue National Contre le Cancer.

The group participates in national and international networks. It also takes a leading role in aCGH studies in a European research network.

- Appreciation on the strategy, governance and life of the research unit

The group mainly appears as composed of three rather independent projects led by independent PI. The leadership of the group leader on genomic studies is clear but the overall added value of having the different projects in the same group is not underlined. Reorganization to highlight the roles of senior investigators should be beneficial.

Collaboration with the breast cancer clinic could be tightened to ensure optimal materials and accelerated clinical validation/application of findings.

Overall, risk-taking appears as limited.

Participation in teaching activities is not documented. Four PhD theses have been defended. Regarding research organization, the group is involved in the establishment of a xenograft platform, and is linked to the vice-direction of the Institute. Regional involvement is achieved through collaboration with the Canceropole.

- Appreciation on the project

The group presents 3 lines of research linked to mechanisms of chromosomal breakage, breast cancer subtypes, and translation into clinical tools. A main historical focus of the group consists of a long-term project around genomic profiling of breast cancer. In that respect refined technologies and collaborative initiatives have been developed. In the mean time, novel medium-term projects around genetic instability and differentiation has been taken on board through new group members.

Plans for resource allocation have not been specified though the group has extensive experiences and a long tradition of support.

Originality is judged as acceptable but could be improved by considering unique angles/approaches e.g. in the application of the xenograft model.

- Conclusion

The evaluation takes the entire research group into account, but herein recognizes heterogeneity regarding the reporting as well as the future potential of the different projects. Several of the issues here raised have also been identified by the group in their SWOT analysis (e.g. lack of local/internal expertise in bioinformatics and rapid technological developments in the area).

The strengths and opportunities include good platforms and knowledge of aCGH, the existing national and international collaborations, the development of a potentially powerful xenograft bank, the presence of two talented researchers developing separate lines of research, the presence of new data that should be prioritized for publication, and the novelty in studies of molecular mechanisms for chromosomal breakage (as potentially central mechanisms for genetic instability linked to fragile sites).

The weaknesses and threats include the group working in a competitive research area and thus need to consider uniqueness, lack of bioinformatics skills, unclear roles/partnerships with seemingly independent members, a need to strengthen collaboration with the clinic in order to allow for evaluation/clinical application. A potential risk is that the group is left behind by other more competitive teams in the field, particularly considering a lack of a clear plan for access to newer genomics technologies. Our specific points will therefore relate to publications, group structure, uniqueness, bioinformatics, and clinical ties.

Publications - Considering the size and the experience of the group, their publications during the last 4 years have been relatively modest, which particularly applies to publications with the group leader as a senior author. It was nevertheless obvious that a lot of new and interesting data, e.g. related to aCGH profiles in breast cancer subtypes, have been gathered. Prioritized publications of these data are therefore strongly encouraged.

Research group structure - The publication record for the group could, however, also reflect a planned transition to new group leaders. The studies related to chromosomal breakage and epithelial cell differentiation are perceived as innovative, focused and scientifically promising. They are run by independent principal investigators that report recent publications of high standards. It should therefore be considered how should these lines of research, which are somewhat disparate from the core of the group program, optimally be continued. There may be arguments for independent group status as well as for remaining in the current constellation, but if the latter applies, the research partnerships herein should be clarified.

Uniqueness - As mentioned, several projects, e.g. breast cancer profiling and establishment of xenograft models, are internationally competitive with a number of well-equipped and well-funded groups running large-scale investigations in the area. The future projects should be designed taking uniqueness into account. Hereunder, the xenograft model is powerful for future therapeutic studies, but needs to carefully ensure that different tumor subtypes will be present. The group should focus on rare subtypes of breast cancer, for which models are not yet available, not to risk ending up with a large collection of basal-like tumors, which would also be available from other groups.

Bioinformatics - Recruiting researcher(s) for development of in-house bioinformatics is essential for the successful continuation of the projects. This shortcoming is recognized by the team leader, and needs to be addressed in order to achieve the goals and to remain internationally competitive. The team would also benefit from development of a plan to ensure access to the latest technologies in genomics.

Clinical ties - The team describes excellent ties to the clinic, which is perceived as a key factor for future studies in breast cancer prognostics and therapeutics. Yet, this aspect should be further strengthened. A closer collaboration could secure clinical samples linked to relevant patient/treatment information, pave the way for prospective analyses of patient samples, and provide possibilities to address the prognostic role of genetic profiles in homogenously treated patient series from clinical trials.

Team E6: Molecular mechanisms involved in resistance to chemotherapy

Team leader: Mr Pierre MARTINEAU

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	4	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	3	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	5	2
N7: Number of staff members with a HDR or a similar grade	5	6

- Appreciation on the results

This relatively large team was created very recently, beginning of 2008. Its main focus is studying the mechanisms of resistance to chemotherapy in colon cancer cells and to develop new therapeutic strategies using an ambitious phenotypic screen of an original scFv fragment library. The team develops unique and highly potent technological approaches that have demonstrated their value for the identification of new intracellular therapeutic targets and of new chemical protein-protein inhibitors. In parallel, clinical studies have notably identified for the first time a molecular signature of the response to FOLFIRI, and in vitro studies have identified several mechanisms of chemoresistance in colon cancer cell lines. Although of interest, the FOLFORI signature has been established on a small number of patients. Its statistical power is at the limit of significance and therefore needs to be improved and fully validated. The group also proposes the development of Imaging Mass Spectrometry to evaluate penetration of the drugs in the tissues.

Together, this has led to the publication of a dozen of original articles by the team itself, a number that has to take into account the relatively high number of researchers with permanent positions (6) in the group. In addition, 25 original papers were published in collaboration. Two clinicians are fully integrated in clinical networks, and promising partnerships have been concluded with biotechs and pharmas for the co development of the technologies. The group has been very active in patent submission and therefore has an interesting patent portfolio in the construction and use of phage-display library (three patents).

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

This is an active team already well-identified by industrial partners for its unique technologies. Interesting patents have been submitted or published. The participation of the team members to congresses and to international consortia will be essential for the attraction of post docs.

- Appreciation on the strategy, governance and life of the research unit

This aspect is difficult to evaluate at this stage since the group was recently created. It is not clear how much the members of the group are involved in teaching or organizational activities.

- Appreciation on the project

The scFv library and the proposal for phenotypic screen are original and, though at risk, of strong interest. The study of the mechanisms of resistance to irinotecan in colon cell lines leads to interesting data on p38 activation and topo I mutations. Its extension to additional cell lines, and possibly to in vivo experiments in immunodeficient animals, is essential to increase its power and significance. The connection with clinical trials is also essential for the validation of these markers. The mass spectrometry-based project on tissue distribution of drugs is of potential interest. However it is presently at a very preliminary, feasibility step. It will hence be important for the group to design a more precise strategy for the use of this technology in well-identified projects. Metastasis and tumour initiating cells are very competitive fields. The authors should more precisely identify what they think is their competitive advantage in such fields. Do they foresee collecting an important number of pre- and post-chemotherapy samples? At this stage the link with scFv and imaging spectrometry is not clear.

- Conclusion

The project of this group is extremely relevant in the context of a cancer centre. The close interaction of scientists with clinicians and surgeons, and elegant clinical approaches constitute an ideal situation to collect valuable materials.

The team has developed elegant reagents and technologies for identifying potential therapeutic targets then drugs. The whole group has to put its efforts to maximally exploit the clinical material through its original approaches and unique powerful technologies which are potential sources of breakthrough innovations.

However, in some projects, in particular those based on the identification of resistance signatures, the members of the group seem to underestimate the need for very large collection of samples to achieve strong statistical powers. Although molecular signatures have been already identified, this young group may not be solid enough to maintain this pharmacogenomic approach (lack of prospective cohorts dedicated to diagnostic marker validation, no pathologist in the group, no bioinformatician).

Recommendation: the group should make every effort to concentrate on a limited number of projects for which they can foresee a strong competitive advantage.

- Team 7: IMMUNOTARGETING AND RADIOBIOLOGY IN ONCOLOGY

  Team leader: Mr André PELEGRIN

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	9	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	3	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	5	4
N7: Number of staff members with a HDR or a similar grade	7	8

  - Appreciation on the results: Relevance and originality of the research, quality and impact of the results

This well-established team is developing projects on radio-immuno-targeting (imaging and radio-immunotherapy, R.I.T.), antibody engineering and evaluation of new targeted therapies in oncology, mostly based on the use of recombinant antibodies. Over the years, the team has established a strong relationship with clinicians from the Cancer Center. In addition, it has gained a strong expertise in the use of therapeutic antibodies in tumor animal models. The major contribution of the team has been to propose a combined use of monoclonal antibodies directed against HER-2/Neu and EGF-R. A Proof-Of-Concept (P.O.C.) has been made in two mouse models, making it possible to initiate a Phase I-II clinical study in metastatic pancreatic cancer patients (involving both Roche Pharma and Merck AG). A patent on the combined use of two anti-HER-X (X being 1, 2, 3…) has been deposited. Another important contribution is the development of an original model of the anti-Müllerian Hormone Type II receptor (AMRH-II) by the team. This a very promising theme, as the target (for ovarian cancer) is original, a proprietary monoclonal antibody having being generated by the team and a company being interested by developing the antibody for therapeutic use. Last, the team has proposed a new R.I.T. strategy for solid tumors, based on the use of antibodies labeled with low energy electron emitters (Auger emitters). Overall, the results are fully relevant with the medical and scientific environment at the Montpellier Cancer Center, and rather original at least for the data summarized above. However, there has been a tendency to work on too many topics instead of focusing on and exploring in more details the most original, less competitive subjects. It has certainly impacted the level of publications. Although regular and clearly anchored in the field of antibody and radiobiology, the publication list is qualitatively modest with regard to the size of the team (10 permanent scientists). Among 17 publications of the team, four have been published in journals with impact factors higher than 5. Members of the team have collaborated in 47 publications. Three patents have been deposited (EPO) since 2005. Although no licensing/commercial exploitation agreement has been signed so far, the patent concerning the combined use of anti-EGFR and anti-HER2 antibodies should be strongly and aggressively defended by the relevant french agencies (INSERM-Transfert, FIST, Universities Industial Property Department…). A small start-up company (SurgiMAb) has been set up, based on the work of the team that showed that immunophotodetection can be used for intraoperative situations.

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

The team has been able to attract a new INSERM CR in 2008, but no foreign students or visiting scientist from abroad. Also, a good number of french Ph.D. and post-docs are present in the team. No collaboration with teams from abroad is indicated. A multicentric trial is currently performed, initiated by the team, on combination of radiotherapy with targeted therapy using antibody in locally advanced rectal cancer.

- Appreciation on the strategy, governance and life of the research unit

The team is large, including 10 scientific investigators among which 3 clinicians. The coordination and complementarity between the different scientists within the team are good, with different scientists participating in different projects. However, the team is rather isolated, relative to the other teams of the IRCM. Also, the external scientific communication at a national and international level should be implemented. Scientists from the group have been successful in obtaining grants from the INCA, the PHRC, the ANR and charities. The surgiMab company is strongly supported by a grant from ANR.

- Appreciation on the project

The scientific project is a therapy-oriented project, with translational interest. The main focus of the team is to use antibodies, peptides and derived molecules to treat solid tumors. There is also a radiotherapy/radiobiology project that, although being apart, is important in terms of clinical value and insertion of the team within the Montpellier Cancer Center. One part of the project is devoted to the analysis of the mechanisms of action of therapeutic antibodies (receptor heterodimerization and targeting molecules into lipid rafts), while the other part is focused on the generation and evaluation of different antibody formats to treat solid tumors (anti-idiotype, radiolabeled antibodies, combined use of antibodies …). The project on the targeting of AMRH-II is competitive in terms of target and can be of high value for the treatment of ovarian cancers. Similarly, the project on the use of Auger electron emitters is original and should be reinforced with regard to its link with clinicians. Some of the projects could lead to cutting edge data such as the study of antibodies that specifically modulate the clustering of target molecules into membrane rafts and the deciphering of the underlying molecular mechanisms of their action. However, its feasibility is intermediate, due to the high number of tasks and of different topics. The different projects should therefore be ranked in terms of priority. The originality and risk taking is average for this large team. The immunology projects deal with the generation of new antibodies and immuno-conjugates and with the understanding of their mechanisms of action. Some of them (targeting AMRH-II, use of antibodies coupled to electron Auger emitters, lipid-raft molecule targeting) are internationally competitive due to the know-how and skills of the team and their strong links with clinicians of the Montpellier Cancer Centre. They are clearly translational-oriented and, with regard to this, can be of high value.

- Conclusion

This is a well established team that has been skilful to develop useful tumour mouse models to investigate the "Proof-of-Concept" of newly generated antibody formats designed in house or in collaborations. It has been also able to build-up close links with clinicians of the Montpellier Cancer Centre as well with several biotech/pharma companies. Several funding from national agencies (ANR, INCa) and from private companies have been obtained.

The team has developed a large program of research on many subjects ranging from the combined use of monoclonal therapeutic antibodies in two models (HER2/EGF-R/HER-3… ; AMHR-I and AMHR-II), idiotypic vaccination, antibodies coupled to Auger electron emitters … etc) to membrane raft targeting, RGD cyclic analogues for targeting angiogenesis… etc. Several clinical developments are underway or will be initiated in a near-future. Also, it has close links with biotech/pharma companies that should be maintained and strengthened since many of the topics are related to pre-clinical and clinical research projects. It has also good links with clinicians specialized in radiotherapy and radiobiology. The project on electron Auger emitters and antibodies is a good opportunity to still strengthen the links.

The main weakness is the large number of topics that should be reduced or at least ranked for high, medium or low priority. Clearly, the team and its leader should concentrate their efforts on the most promising subjects for which the team is internationally competitive, and deepen the cellular and molecular analyses of the selected topics. This should enable the team to raise its level of publications and its presence in international meetings and conferences (posters, oral presentations) and hence to reach the international recognition that it deserves. More integration within the IRCM could be achieved by setting up a collaboration dealing with receptor heterodimerization /lipid rafts targeting and signal transduction for instance.

Three main recommendations can therefore be made :

- The number of projects should be reduced/prioritized and team efforts should focus on topics for which it is internationally competitive. Projects should be more focused, and explored in a more detailed manner in terms of cellular and molecular mechanisms.

- Relationships with other teams from IRCM should be strengthened by setting up collaboration(s) complementary with the prioritized project(s). In particular, the R.I.T. approach on Auger emitters is an original one and should be strengthened, in close collaboration with the Radiotherapy Department of the Montpellier Cancer Center.

- National and international recognition should be increased both in terms of publication level and of presence in national and international conferences.

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A	A

Team 1: HORMONE SIGNALLING AND CANCER

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	A	A	B	B

Team 2: CELL SIGNALLING AND CANCER

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	A	B	B	B

Team 3: CATHEPSINS, AUTOPHAGY AND CANCER

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A	A

Team 4: MOLECULAR BASIS OF CARCINOGENESIS

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	non noté	A	A+	A+

Team 5: TUMOR IDENTITY AND PLASTICITY

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	B	A

Team 6: MOLECULAR MECHANISMS INVOLVED IN RESISTANCE TO CHEMOTHERAPY

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A	A

Team 7: IMMUNOTARGETING AND RADIOBIOLOGY IN ONCOLOGY

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A	A

Administration Droit Economie Gestion Médecine Odontologie Pharmacie Sports

Université Montpellier 1

Montpellier, le 12 mars 2010

Le Président
Ph A/ NG
Départ n° 2010 - 85

Monsieur Pierre GLORIEUX
Directeur de la section des unités
de recherche
Agence d'Evaluation de la Recherche et de
l'Enseignement Supérieur (AERES)
20, rue Vivienne
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Monsieur le Directeur,

Je m'associe aux remerciements formulés par l'ensemble de la direction de l'unité de recherche **«Institut de Recherche en Cancérologie de Montpellier»** pour la qualité du rapport d'évaluation fourni à l'issue de la visite du comité d'expertise.

Vous trouverez ci-joint les réponses du Directeur de l'unité auxquelles le Vice Président du Conseil Scientifique et moi-même n'avons aucune remarque particulière à rajouter.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de ma considération distinguée.

Philippe AUGE

5, boulevard Henri IV – CS 19044 – 34967 Montpellier cedex 2 – Tel : 04.67.41.74.00 Fax : 04 67 41 74 56

Directeur :
Dr André Pèlegrin
Directeur Adjoint :
Dr Charles Theillet

Montpellier le vendredi 12 mars 2010

Monsieur Jean-François DHAINAUT –
Président
AERES

Monsieur le Président,

Veuillez trouver ci-joint notre réponse à l'évaluation de l'Institut de Recherche en Cancérologie de Montpellier (IRCM ; Inserm U896) réalisée en décembre 2009 par l'AERES.

Je vous prie de recevoir, Monsieur le Président, l'expression de mes salutations distinguées.

André Pèlegrin
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Comments concerning the Institute

We thank the committee for its in-depth analysis of the activity of our Institute. The committee underlined our objective "to establish a strong potential in cancer research within a clinical cancer centre with the aim to create a comprehensive cancer centre as they exist in the US" and the fact that this evaluation takes place only two years after the establishment of the Institute.

Our reply is based on the weaknesses pointed out in the report and the related recommendations made by the committee.

Recommendation 1

"To increase focus and to define research priorities and plans for future developments. To limit the number of separate projects within each team by at least 2 folds. Focusing on a smaller number of topics will help to reach more visibility and higher impact of publications that originate from the IRCM teams."

The issue of the numbers of separate projects within each team has been discussed in depth with all the team leaders who globally agree with the recommendation and proposed prioritization of their projects.
The issue of increasing the focus and the definition of research priorities for the future at the Institute level will be addressed as part of our calls for new research group applications.
Our first call (deadline March 2010) has still a broad scope being defined within our "Molecular targets and cancer therapeutics" frame. Our aim was to attract talented young scientists and we did not want be too exclusive. However, we will focus our second call.

Recommendation 2

"To have a better integration of the different projects within each team and to provide incentives for collaborations within and between teams"

As indicated, this issue has been discussed in depth with all the team leaders who globally agree with the recommendation and proposed prioritization of their projects.
The number of publications involving 2 or more groups of the Institute is not high yet (14) but this is mainly due to the recent establishment of the IRCM. It is noticeable, however, that the number of collaborations between different teams is currently on the rise.

Recommendation 3

"To strengthen the external communication of the Institute, in particular through an updated and complete English version of the web site and through more participation to international meetings."

We agree that our web site which was settled up in 2007 was updated regularly only in French. The English version will be updated and completed in the next two months.
Participation to international meetings will be encouraged with a potential financial contribution of the Institute for the support of young scientist. However, it must be realized that meeting participation is the first expense to be cut down when funding is short.

The external communication will also be strengthened by increasing the number of guest speakers from abroad for a seminar at the Institute. The dedicated budget has been increased and we recently agreed to invite on a more regular basis (every other month) "very high level foreign scientists" for seminars in order to increase the IRCM notoriety both locally and internationally.

Recommendation 4

"To attract young scientists through competitive international calls."

This point has been partly addressed as part of our reply to recommendation 1. We want, however, to stress that response to our international call is clearly positive. Although the deadline is March 31 we already received 11 relevant applications (3 from USA, 2 from UK, 2 from Germany, 1 from Italy and 3 from France). Some of the candidates have already been invited to give a seminar. We are thus confident that this call will allow the recruitment of at least two international standard groups.

As a starting package, every new group will be offered lab space, tax (overhead on contracts) exemption, a priority on the mobility of technicians and engineers and free access to the Institute lab store. In order to increase our attractiveness, we decided to provide basic lab equipment. Such conditions are equivalent to an "incubator lab" and seem optimal for young group leaders in emergence. It will be attributed for a maximum period of 2 years allowing the renewal of such incubation operation for a new candidate. The budget is available and this "incubator lab" will be ready by the end of June 2010. Furthermore, we are considering the possibility of a starting grant that could be allocated to a particularly promising candidate.

Furthermore and following a proposition of the "Cancer" ITMO, a "chaire mixte" supported by Inserm and University Montpellier 1 has been attributed to IRCM. This new permanent position is an opportunity to attract a new young scientist by the end of September 2010.

Recommendation 5

"To define a clear process for the internal promotion of new team leaders."

This process is clearly defined and formalized in our internal rule chart (réglement intérieur) but was apparently insufficiently detailed in the documents provided to the committee. These rules were applied to Emmanuelle Liaudet-Coopman who started an emerging group and who is currently developing a fully independent team. We want to emphasize that internal candidates are evaluated competitively with external candidates. In this respect, candidates present their projects in a written document and during an oral presentation in front of the whole Institute. The project is discussed among team leaders and, in case of a positive evaluation, the project is sent for further advice to our International Scientific Advisory Committee.

Once selected, candidates benefit of an "emerging group" status during the time they need to apply to an AERES / Inserm evaluation. The details concerning this status and the support of the Institute to the group is discussed for each case depending on its precise situation.

Recommendation 6

"To strengthen the links with clinicians of the Val d'Aurelle cancer centre, in particular with the pathology department and with local or regional routine molecular pathology labs."

This recommendation has been discussed with the Director of the Val d'Aurelle Cancer Center and the Medical Adviser (see attached note). They both took good note of these comments and have given us assurance to actively work on this and give rapid repercussion. As a starting action a committee mixing the heads of the pathology department, routine molecular pathology lab, hospital pharmacy and the IRCM director and deputy director has been set up with an aim to optimize working relations and facilitate translational projects involving all parties. Furthermore, the involvement of clinicians in research has been considered an essential issue and means to give more time off the clinics a priority.

Recommendation 7

"To open the IRCM to the regional, national and international scientific communities."

IRCM has multiple connections to the regional scientific community and is playing a pivotal role in the recently set up "Montpellier-Cancer" association gathering laboratories working on cancer in Montpellier. IRCM is also deeply engaged in the Canceropole GSO, with several of his senior staff being either involved in steering committees or networks. It plays an important role in local technological platforms such as Montpellier Animal Facility Network (RAM); Montpellier Genomix (with the array-CGH platform); Animal histology.

At the national level IRCM is highly active in the Carte d'Identité des Tumeurs Program as well as the translational research group of the Fédération des Centres de Lutte Contre le Cancer.

Additional efforts will be made to increase this point.

Recommendation 8

"To recruit at least one bioinformatician. Being connected with bioinformatic labs or platforms in Montpellier or elsewhere is important but given the evolution of profiling technologies it is mandatory to have in house expertise."

We fully agree with this comment. The absence of bioinformatics at the IRCM is a serious problem that is recurrently pointed at by our International Scientific Advisory Board. Some temporary solutions have been found in the past by some teams, but due to the absence of long term position could not be secured.

However, we have been actively working on this point for over two years. Currently two actions have been taken:

1. In house reconversion of a senior researcher (Patrick Augereau), who is a trained molecular biologist with 20 years of experience at the bench, but has also good training in math from his university years. Patrick Augereau has started training in this field.
2. Hiring of a senior scientist at the group leader level with a high level of expertise in bioinformatics. Our idea is to hire a biologist with a strong background in math and statistics, that could serve as a node in a network linking colleagues working in statistics or math departments on related questions that might want to develop models on biological datasets. We have identified such a person, who would be interested to join IRCM. We are currently discussing this issue with the University, who seems interested by the idea of hiring, at the professor level, a candidate that would form a bioinformatics group.

These actions are consonant with the planed arrival of a new leader of the biostatistics unit at the CRLC in June 2010. The CRLC has agreed to hire a candidate with experience in this field.

Recommendation 9

"To strengthen in house pathology support"

The house pathology platform has been supported in 2009 and the effort will be maintained. There is a clear consensus between all the research teams concerning the usefulness of this platform. We are currently in discussion with a veterinarian who has deep expertise in anatomo-pathological analyses of murine models, and who is willing to move to Montpellier. Her arrival would undoubtly strengthen our "in house" expertise necessary for the analysis of our numerous cancer-related mouse models.

Recommendation 10

"To participate in the steering committee of the Val d'Aurelle centre"

This has been discussed with the Director of the Val d'Aurelle centre who agreed.

Comment concerning our International Scientific Advisory Committee (ISAC)

The AERES committee regretted that the recommendations of our International Scientific Advisory Committee (ISAC) were not made available to them. This was done according to our policy for 2 main reasons. First, we ask to our ISAC to be very stringent with us to really underline the points which need to be improved. Some of these comments are made only to the head of the unit. Second, and even more important, the ISAC site visit and evaluation was made in April 2009 based on a preliminary project sent in March with the aim to strengthen the project before submission to AERES.

Team E1 : Hormone signalling and cancer

Team leader: Mr Vincent CAVAILLES

We thank the evaluation committee for its constructive report and appreciate the comments in relation with our scientific project and the organization of our team. We accept most of the criticisms and will do our best to further improve the ongoing evolution of our group.

Specific replies

- Appreciation on the results

Concerning the quality of our publications, although we agree that we should improve the impact factors of the journals in which we publish, we would like to mention that amongst the 21 original manuscripts primarily arising from our group and published from 2004 to 2009, 6 (and not 4 as mention in the AERES report) have an IF>5 according to the *Journal Citation Reports* database.
It should also be noted that 1/3 of these articles (7 publications) were published in speciality journals corresponding to the Environmental Sciences category. According to the *Journal Citation Reports* database, the best of these journals (on a total of 163) is ranked with an IF of only 7.4 and one of our papers was in Environmental Health Perspectives which is ranked 2/163.
Finally, 12 other papers corresponding either to reviews (Pharmacological Reviews, Trends in Endocrinology and Metabolism) or collaborative works (Nature Genetics and very recently, in Nature Structural and Molecular Biology) were also published by our group in journals with an IF>5.

- Appreciation of the links with international, national and local partners

We welcome the recommendation that the committee made to increase participation to international or national scientific networks.
However, we would like to remind that our lab is already involved in a European Excellence Network which encompasses 23 laboratories from 9 countries. At the national level, we have been involved in two Networks supported by INCa (ResisTH network) and ARC. Finally, our strong and effective collaboration networks are highlighted by the number of collaborative papers (35 articles from 2004 to 2009).

- Appreciation on the strategy and governance

As noted by the committee, all the projects currently being developed in the group are organised around the theme of nuclear receptors signalling.
We think that there is a clear coherence in the team projects with focus on hormone signalling in cancer at three levels: ligands, receptors and transcriptional coregulators. As mentioned by the committee which appreciated the “multidisciplinary nature of the group”, these aspects are developed through cognitive, applied and translational projects. We will obviously pursue our efforts to strengthen the overall coherence between the scientific projects, the use of the screening platform and the clinical trials.

Although the name of the different permanent scientist in charge of the four main projects of the team (Characterization of receptor ligands, role of estrogen receptors in hormone-dependent cancers, HDAC and estrogen signaling, role and mechanism of action of RIP140) were clearly mentioned in the written project and during the audition, we agree that their precise role and responsibility might have been more precisely clarified in some cases.

- Perspective for the future of the modulator screen platform

Concerning the transcriptional modulator screen platform, we appreciate to hear that it constitutes one of the main strength of our group. This platform and the associated industry-sponsored projects have been used both for ‘contract research’ and to further develop our scientific aims. For

instance, the contributions of our group in two very recent collaborative papers published in EMBO report and Nature Structural and Molecular Biology were done by people paid on these industry contracts. In addition, several bioluminescent tools that we have set up for the industry have been used by our group to answer some of the scientific questions that we raised. Another goal is to provide the scientific community with powerful tools (two reporter cell lines developed by the platform are in the terminal phase of validation by the European Community Validation Alternative Methods, ECVAM)
Very recently, we have initiated a discussion within the institute, to pool all the expertise and equipment in a more global cellular screening platform. This will increase the visibility of the platform and facilitate the acquisition of new equipments.

- Appreciation on the project

As noted by the committee, we have initiated collaborative efforts with the hospital and these links will be reinforced. Two clinical studies directly related to the main scientific aims of the group are submitted for publication or in preparation.
Moreover, as suggested by the committee, we were aware of the necessity to improve the focus in addressing the scientific questions. This has been already undertaken and we have defined the projects which will be either terminated (BrCa1 and ER expression) or refocused on the RIP140 problematic (HDACs and ERβ) at the end of 2010. We believe this prioritisation will increase the overall visibility of our group and improve our competitiveness on an international level.
Finally, we also agree to consider addressing the scientific questions in a more global fashion. We would like to mention that we already tackle this problem at the transcriptomic and genomic levels (unpublished data obtained in collaboration with the Affymetrix and CGH array platforms). However, this has been quite limited until now due to the lack of bioinformatics competences in the team. As recommended by the committee, the recruitment of a bioinformatician would allow in house expertise and facilitate such global analysis.

Team E2 : CELL SIGNALLING AND CANCER

Team leader: Mrs Dany CHALBOS

We have noted the recommendations and advices of the expert committee and we will consider them seriously.

We do not believe that the group has been destabilized by the departure of two permanent scientists. On the contrary, we think that its new organization will lead to an increased cohesion and allow the constitution of a team more focused on cell signaling in triple-negative cancer. In addition, it is both natural and good that younger scientists develop their own group. Moreover, we have recruited a talented young scientific with a great experience in dissecting pathways controlling invasion which is very appropriated for the project that we want to develop.
This small team allows many interactions between people who all discuss all projects and contribute, according to their competence, to some developments of the different programs. The expert committee has noticed than in the past format, most publications do not associated different PIs from the group. It is and it will be less and less the case for the PIs involved in the current team.

We want to precise that most of invitations to present work in meetings and organization of conferences, considered by the expert committee to clearly show a local and national visibility, were on the behalf of the researchers of the new group. We agree that the international visibility of the new group is relatively modest although international collaborations have resulted in 5 collaborative publications with US, UK, The Netherlands and Belgium (2 MCB, Nat Cell Biol, J Cell Science, Int J Biochem Cell Biol). The Oncogene publication on Fra-1 (2005 which was relatively well cited with 61 citations) is at the origin of strong and productive national and international collaborations. These collaborations will continue in the future. In particular, a manuscript in collaboration with G Sonenshein (Boston) concerning the AP-1 regulation of blimp-1, which down-regulates ERα expression, is in preparation and this productive collaboration encourage us to present a common project to get funding from the US department of defense breast cancer research program.

Some projects appeared at relatively low risk perhaps because there are now well advanced. Indeed, one of them and part of a second are now terminated. For the future, we will follow the recommendation of the committee and plan to develop more large scale methods in particular proteomics. These points are developed below.

Specific replies

We agree that the studied genes and pathways are of potential interest for several types of cancers and probably, at least for some of them, for several breast cancer sub-types (it is in particular the case for PTPL1 whose interest could be also important in the HER2 sub-group and for the sensibility to antiestrogens of ER+ tumors). However, we will give priority to projects aimed to test their interest in triple negative tumors. Concerning Fra-1, a transcriptome analysis of 1021 primary breast tumors recently confirmed our results obtained in breast cancer cell lines ie the reverse correlation of Fra-1 with ERα and its high expression in triple negative tumors (C Theillet, IRCM, personal communication). Indeed we have shown that Fra-1, as Fra-2, is negatively regulated by ERα (Nature Cell Biol, 2007). Conversely, in the same transcriptome study, PTPL1 expression was very low in this group of tumors in agreement with our pilot study (Int J Cancer, 2009) which has shown that the enzyme high expression level, which is an independent factor of good prognosis in breast cancer, is positively correlated with ERα expression. β-catenin and src pathways are studied on account of their relation with PTPL1 and Fra-1, and their implication in cancer progression. An inverse correlation with ERα is observed for increased level and/or activity of Src which are frequent in primary breast cancers and the response signature of Dasatinib, a kinase inhibitor targeting Bcr-Abl and Src family kinases, was most prevalent in triple-negative cell lines which are indeed more sensitive to inhibition of proliferation (Fin RS, 2007; Huang F, 2007). Several phase II clinical trials are now under way in different breast cancer subtypes and in particular in triple-negative tumors. Concerning β-catenin, an increased cytoplasmic and nuclear β-catenin level is found in many

cancers including breast cancer and is an independent marker of poor prognosis. It is however not specific to triple-negative cancers but the maintain of β-catenin in the nucleus by Fra-1 could take an important part in the Fra-1-induced transcriptional program leading to an aggressive phenotype.

We are aware that links with clinician implicated in this field are essential. We have now a collaboration and frequent discussions with Dr William Jacot, medical oncologist at the Val d'Aurelle cancer center, who is particularly implicated in the management of triple negative cases.

As recommended by the committee, we are convinced of the necessity to improve the scientific focus. As noted in the project report, our priority projects concerned the regulation of the Src pathway by PTPL1 and the control of Fra-1 expression and activity by PKCθ. Since its writing, we identified PTPL1 as the first phosphatase able to inhibit Src activity, which has been shown to be elevated in triple negative cancers, through direct dephosphorylation in intact cells. A manuscript is in revision for Cancer Research. This project is therefore terminated and our priority is now to define the regulation of PTPL1 activity by phosphorylation in the aim to up-regulated expression and/or activity of PTPL1 which would be of considerable potential interest in particular in triple negative cancer in which PTPL1 expression is low. Concerning Fra-1, we have now establish that PKCθ, which is only detectable and present in an active form in breast cancer cells which do not express ERα, stabilizes the Fra-1 protein and increases its biological and transcriptional activity and a manuscript is in preparation. Our priorities are now to test the efficacy of specific PKCθ inhibitors on growth and metastasis dissemination of triple negative breast cancer cells xenographs and to determine the molecular mechanism underlying PKCθ-induced Fra-1 activity. We also plan to develop antibodies to test the interest of phosphorylated Fra-1 and/or PKCθ as a prognosis marker in breast cancer. To summarize, our main objective will be therefore to determine how the phosphorylation regulates the expression and\or activity of both proteins which might ultimately lead to the proposition of new therapies based on kinase inhibitors.

We agree with the committee that national and international collaborations on the field of triple negative breast cancer and participation to international or national scientific networks should be developed. Indeed, the integrative network RésisTH, which implies basic research teams and 5 clinical research team, has now evolved and been extended more generally to "Translational research in breast cancer".

Concerning the consideration of unbiased large scale method, we plan, as noticed in the project report, to use quantitative mass spectrophotometry after iTRAQ labelling combined with substrate trapping to identify a large spectrum of substrates of PTPL1. Results recently obtained on the increased activity of Fra-1 by PKCθ encourage us to consider the comparison of the transcriptome and of the interactome of Fra-1 phosphorylated or not by this enzyme. This studies will be possible thanks to our engineered cell systems recently established. In addition, a collaborative study is planed with the group of Marc Piechaczyk (IGM), a specialist of FOS proteins which is, based in particular on our results, developing ChIP-on-chip experiments on triple negative breast cancer cells (where Fra-1 is hyperphoshorylated) to identify the DNA sequences occupied by Fra-1, to study the role of PKCθ on selected target genes.

Two candidates to a permanent position, jointly supported by Inserm and UM1 and attributed to IRCM, with competences in proteomics have contact us. The recruitment of one of them would be therefore invaluable for some parts of our project.

Team E3: CATHEPSINS, AUTOPHAGY AND CANCER

Team leader: Mrs Emmanuelle LIAUDET-COOPMAN

We would like to thank the AERES committee members for their encouraging comments concerning our project. We will take in account the constructive advices from the AERES committee members.

Concerning the publications of the PI, another one has been published in *PlosOne* in 2009 (Masson et al., *LRP1 receptor controls adipogenesis and is up-regulated in human and mouse obese adipose tissue*, PlosONE 2009, 4:e7422), one is in revision at *Mol Endo* (Olivier Masson et al. with the PI as last author, *Cathepsin-D, a key protease in breast cancer, is up-regulated in obese mouse and human adipose tissue and controls adipogenesis*), and 3 manuscripts are in preparation.

One Thesis has been successfully achieved in the 2004-2007 period (Mélanie Beaujouin). A second Thesis has also been successfully achieved in the 2007-2010 period (Olivier Masson).

It is important to point out that our team financed 3 post-doctoral positions during the 2004-2009 period:
2005-2006 : Murielle Glondu-Lassis (financed by AFR in collaboration with G Berchem by Luxembourg),
2007-2008 : Valérie Laurent-Matha (financed by ANR "*Jeunes chercheurs Jeunes chercheurses"*),
2007 (6 months): Mélanie Beaujouin (financed by EU Chemores).
We will recrute a post-doctoral fellow if the ANR "*Jeunes Chercheurs Jeunes Chercheuses"* submitted by Sophie Pattingre is accepted.

We agree with committee that it is crucial that the team obtains new funding. Sophie Pattingre applied to ANR "*Jeunes Chercheurs Jeunes Chercheuses"* in January 2010 (300 000 euros). We will apply to ARC GSO (16 000 euros) in Mars 2010, to ARC *"Subvention fixe"* (50 000 euros) in summer 2010.

To strengthen the relationships to other groups specialised on lysosomal proteases, we are developing new collaborative works with a specialist of cysteine cathepsins (G Lalmanach, Inserm U618, *Protéases et Vectorisation Pulmonaires*, Tours, France).

Moreover, to support the interactions with international clinical groups, we just obtained an AFR thesis financial for the PhD student Salwa Sebti in collaboration with Guy Berchem, a MD-PhD specialist of apoptosis and autophagy that is the head of the "Laboratoire d'Hémato-Cancérologie Expérimentale" at "Centre Hospitalier du Luxembourg".

Team E4: Molecular basis of carcinogenesis

Team leader: Mr Laurent LE CAM

There is no specific reply regarding the overall evaluation of our young group.

Regarding the potential threat about limitations in mouse housing, we would like to reinforce this specific point and point out that there is an ongoing evaluation about a possible extension of the IRCM mouse facility. Rapid implementation of this project is mandatory for our research projects as well as for new groups that will join the IRCM in the coming years.

Other advices of the AERES committee will be implemented in the coming years.

Team E5: Tumor Identity and Plasticity

Team leader: Mr Charles THEILLET

We want to thank the evaluation committee for its thorough examination of our activity and helpful comments. Some points, however, need either to be amended or better explicited on our side. These concern price and distinctions, structure of the group and interconnection of the projects, future plans, present publication record and evolution of the team.

- ### Price and distinctions

We want to correct an oversight in the original report. PI members in the team have been awarded prices or distinctions

Arnaud Coquelle
Lauréat chercheur d'avenir du Languedoc-Roussillon 2009
Article selected as "fait marquant" in the Inserm annual report 2009 (Nature Cell Biol, 2009)
Charles Theillet :
Prix du Ruban Rose recherche fondamentale 2006

and invited for seminars or talks abroad.
Charles Theillet :
2006 NCI, Bethesda, USA, invitation Bob Callahan ;
Vienna University Hospital, Austria, invitation Robert Zeillinger
2007 ISREC Lausanne, Switzerland, invitation, Cathrin Brisken ;
FMI, Basel, Switzerland, invitation, Nancy Hynes
2009 Royal Marsden, Breast Cancer Breakthrough, London, Jorge Reis-Filho

Organizer of the 10th European Workshop of Molecular genetics and Cytogenetics in Solid Tumors, La Grande Motte, 2006

Pierre Savagner
2005 NIEHS, Research Triangle Park, NC. Invitation: S. Akyiama
UNC, Charlotte, NC. Invitation: K. Bost
2006 NCI, NIH, Bethesda MD USA. Invitation: DS Salomon.
2nd TEMTIA meeting Vancouver, Canada
2007 Stem Cell Research, Nice, April 20-23, France
2009 Uppsala Swedish University of Agricultural Sciences
Séance commune Académies Sciences et Médecine, Paris : La plasticité cellulaire
Journée Paul Basset, IGBMC Strasbourg
4th TEMTIA meeting, Tucson AZ USA
Carrefour Pathologie, Maison de la chimie, Paris

Organizer of 3rd TEMTIA meeting Krakow Poland 2007, EMT France, Lyon, 2008

- ### Structure of the group and interconnection of the project

It is noted that our team gathers three PI developing independent projects. We agree on this assessment. However, it is also mentioned that the project are "disparate" and that "the team has taken on board new PI". These points need correction.

Our team has been created in 2007 and all three PIs (Arnaud Coquelle, Pierre Savagner, Charles Theillet) were part from the start. This was based on shared scientific interests which will be developed hereunder. It also fitted INSERM requirements which favored teams counting at least 10 people. This implied to limit the number of projects and work on their convergence. It may not

have been totally clear to the committee that Arnaud Coquelle started his project while joining the team and that Pierre Savagner reoriented his scope (see below).

Shortly, three examples of convergence:

1. Pierre Savagner, who historically worked on Epithelio-Mesenchymal Transition in skin models has moved his interest to the morphogenesis of the mammary gland. This has led him to acquire expertise in delicate approaches such as cell implantation in a cleared mammary fat pad and isolation of cell fractions able to reform a full mammary gland. This approach is in clear convergence with the general aim of the group which is interested in characterizing the determinants of breast cancer subtypes.
2. The approach developed by Pierre Savagner is in full consonance with that set up under the direction of Charles Theillet aiming at developing a collection of breast tumor xenografts. The expertise in mouse mammary gland morphogenesis will be of great help to improve the take of rare or dolent subtypes.
3. The second project developed along these lines concerns the establishment, as part of a project funded by ANR, of transformed hMEC (from primary cells established in the lab) to study epigenetic and genetic changes associated to early steps of cancer transformation. These models will be valuable tools for other studies either in vitro or in vivo. In vitro they will be crucial for Fragile site determination, in vivo they will be interesting in mammary fat pad grafting experiments.
4. Arnaud Coquelle and Charles Theillet have common interest in characterizing mechanisms at work in the onset of aberrant chromosomal breaks. In this respect, they joined forces to devise and produce a BAC-array covering common fragile sites. This "Fra-site" array is currently being used to study DNA replication dynamics in these regions in cells with impaired DNA replication stress signaling.

In conclusion to this point, we understand the fields we cover may be considered as broad, however, we want to point out that it is our experience that this has led to rich scientific reflection and fruitful cooperation.

- Future plans

Genomic profiling

The report expresses some surprise about the lack of clear plans concerning high resolution genomic profiling, such as high throughput sequencing. The question of next generation sequencing at the IRCM is developed in another section of this document. However, we apparently did not make clear that we plan to move our scope away somewhat from systematic genetic profiling of clinical material and embark on hypothesis based projects.

These projects are being developed along two lines:

1. Primary epithelial cell culture from human (as described above) and mouse mammary gland that are conditionally transformed.
2. Focused studies based on well characterized breast tumor xenografts. These studies will stem from hypotheses developed on large scale genetic profiling data that we have produced as part of the "Carte d'Identité des Tumeurs" (CIT) program. To develop these projects we will take advantage of bioinformatics analyses that we have performed with the CIT bioinformatics team, as well as on future analyses based on functional modules.

Genetic profiling will be part of these projects, as will be high throughput sequencing, but we foresee to downsize these orientations in comparison to former projects.

Bioinformatics

The absence of in house bioinformatics support is repeatedly pointed as a serious shortcoming, both at the level of our team and at that of the IRCM. We fully agree on this. The team had hired a young bioinformatics engineer that left for a permanent position in a local agricultural research agency. His departure has badly struck us and seriously hampered ongoing projects. Nevertheless, we plan to correct this both at the level of the IRCM (see general section) and in our team, as we are in

advanced discussion with a colleague (senior researcher at INSERM) currently working in Strasbourg who wishes to join our team to develop bioinformatics based projects. Furthermore, given planed reduction of the activity on the genomic array platform, Beatrice Orsetti (Cancer Center Engineer in charge of the platform) is currently acquiring training in the bioinformatics field.

- Publication record of the genomic profiling group

Publication record is considered as modest and it is clearly a fact. It is also noted that the group has generated a very large body of data that the committee urges to publish as soon as possible.
We would like to reassure the committee that we are very actively working on exploiting the data we have generated and writing up papers. First papers in line concern the molecular classification of breast tumors for which we have assembled data on 700 tumors in the discovery set and 2300 tumors from public data in the validation. Data are exciting and of high potential. The paper concerning the impact of genetic instability in colorectal cancer is also very much advanced. These are first of a series. However, in our defense we want to point out that these projects all involve consortia with a large number of collaborators. Such consortia are difficult to handle and move slowly.

- Evolution of the team

This point brings us back to the structure of our team based on three PI enjoying a good level of independence, leading to the supposition that we have plans for the emergence of new group leader. This point is part of a mutual understanding and regularly discussed. Emergence will clearly occur within the next four years and/or at the end of the next four year term.

Team E6: Molecular mechanisms involved in resistance to chemotherapy

Team leader: Mr Pierre MARTINEAU

- Appreciation on the project

"The study of the mechanisms of resistance to irinotecan in colon cell lines leads to interesting data on p38 activation and topo I mutations. Its extension to additional cell lines, and possibly to in vivo experiments in immunodeficient animals, is essential to increase its power and significance. The connection with clinical trials is also essential for the validation of these markers."

We plainly agree with the Committee's comment on our current results on p38 activation in cell lines. We have already extended our project to several cell lines, to animal models and to clinical data. The future of the project will be decided in light of the data obtained using these approaches, and particularly the analysis of human tissue samples which is currently ongoing in collaboration with the pathology department of the hospital.

"The mass spectrometry-based project on tissue distribution of drugs is of potential interest. However it is presently at a very preliminary, feasibility step. It will hence be important for the group to design a more precise strategy for the use of this technology in well-identified projects."

This is indeed a very important questions we have started to address. Our main investment in the last year has been to develop and secure this very interesting technology within the group. A first paper has been published and we are now capitalizing on these first results. We are currently setting up a collaborative project based on this technology with the main objective of optimizing the HIPEC to increase efficiency and decrease side toxicity. Several surgeons involved in HIPEC development (F. Quenet, CRLC Montpellier; P. Sugabaker, Washington Hospital Center, USA; D.L. Morris St George Hospital, Melbourne AU; O. Glehen, Lyon; S. Gonsales-Morano, Madrid ESP) have manifested their interest in such a program. Analysing drug tissue penetration should allow to determine the best drug for each cancer type HIPEC compatible and the optimal drug exposure time to obtain the best efficacy/toxicity ratio.

"Metastasis and tumour initiating cells are very competitive fields. The authors should more precisely identify what they think is their competitive advantage in such fields. Do they foresee collecting an important number of pre- and post-chemotherapy samples? At this stage the link with scFv and imaging spectrometry is not clear."

We do agree that this field is highly competitive but it also opens the possibility to publish at higher level in the best journals of the field. We have carefully evaluated what are our strong points that may allow us to tackle this subject differently from the other groups. We will indeed collect pre- and post-chemotherapy samples but because of the difficulty we will be limited to a rather small number of pre-chemotherapeutic tumours. We have thus devised a multi-step strategy based on the analysis of a limited number of pre/post-therapeutic couples followed by a larger analysis of post-therapeutic metastases. One of the main strength of the group is the identification of new markers and targets by use of the scFv phage-display and the imaging spectrometry approaches. Driving the mass spectrometry imaging with informations coming from the scFv screen will allow us to identify new ways to define, then target the cells that survive chemotherapy in metastases.

- Conclusion

"However, in some projects, in particular those based on the identification of resistance signatures, the members of the group seem to underestimate the need for very large collection of samples to achieve strong statistical powers. Although molecular signatures have been

already identified, this young group may not be solid enough to maintain this pharmacogenomic approach (lack of prospective cohorts dedicated to diagnostic marker validation, no pathologist in the group, no bioinformatician).”

We may have given the wrong impression that we underestimate the need for a very large collection to derive a molecular signature but it is of course not the case. We have been working for several years with the biostatistic group of the hospital headed by Dr. A. Kramar and we have published four papers in the recent years (since 2006) with them (Bascoul-Mollevi C & Kramar A). It is also the case of the pathology department of the hospital (6 papers since 2003 with F. Bibeau).

We certainly do not underestimate the need of a large number of samples but we have been also faced with the difficulty to apply the identified signature in the context of modern therapies that now associate chemotherapies with monoclonal antibody-based targeted therapies. We are currently analysing the validity of our previously determined signature in this context through the analysis of samples collected during an INCa project (Biocolon project). Altogether we will have analysed about 100 samples. I cannot foresee the results but we anticipate that this project will be stopped because of the difficulty to collect samples and to anticipate future therapies.

“Recommendation: the group should make every effort to concentrate on a limited number of projects for which they can foresee a strong competitive advantage.”

It is presumably not clear enough in our project but we have collectively decided to develop only 2 main projects in the next years and to focus our efforts to develop “New therapeutic approaches”. The 2 projects that will be developed correspond to “Analysis of metastatic tissues” (II.2.2) and “Phenotypic screen” (II.2.3) for which we think we have a strong originality. We have started to set-up the 2 projects and the former will start in June and the latter in September.

We hope that these explanations will persuade the committee that our scientific activity will be even more focused in the future and that the goal of everybody in the group is to develop original approaches with clinical applications in mind.

Team 7: IMMUNOTARGETING AND RADIOBIOLOGY IN ONCOLOGY

Team leader: Mr André PELEGRIN

We thank the committee for its evaluation of our "therapy-oriented project with translational interest" and its positive comments. Our reply is based on the weakness pointed out in the report and the related recommendations made by the committee.

Concerning the quality of our publication list, we agree that we should improve the impact factors of the journals in which we publish. However, we would like to mention that amongst the 17 original publications of our team, 6 (and not 4 as mentioned in the AERES report) have an IF>5 according to the *Journal Citation Reports* database (4 Clin Cancer Res, 1 J Immunol, 1 J Nucl Med). Another manuscript has been accepted in December in Annals of Oncology (IF 4.9). Furthermore, 14 publications are in the first quartile of their discipline with some of them in very good place like J Nucl Med which is the number 1 in Radiology, Nuclear Medicine and Medical Imaging.

Based on all our previous works, we agree with the comments concerning the fact that we have a too large number of projects and we would like to stress our decision to reduce them in order to improve our efficacy. This already started at the end of 2009 : (i) the "bifunctional conjugates to stimulate NK cells" project had been stopped in December 2009 with the last PhD defense on this topic; (ii) the "tumor cell targeting using new RGD cyclic analogues" project is also stopped. A submitted manuscript was accepted in March 2010 in ChemBioChem. Valorization of these tools will be made by providing these analogues to others teams interested in the RGD targeting strategy; (iii) the vaccination project using anti-idiotypes antibodies had been stopped in September 2009 (end of the Emergence ANR Grant). This topic is now clearly on the transfer side. We currently have different contacts in order to transfer the project to a company involved in tumor vaccination.
This strategy of focusing on a more limited number of projects is still in progress including the prioritization of the AMHR-2 targeting project with the allocation of additional resources.

The cellular and molecular mechanisms analysis will be stressed thanks to collaboration with others groups at the IRCM and in others Institutes (eg S Roche, CRBM, Montpellier, concerning SILAC technology). Existing links between the Auger RIT projects, the Nuclear Medecine department and the Radiotherapy department will be reinforced in a global radiobiology strategy.

Increased national and international recognition should be achieved thanks to improvement of scientific publications level. To strengthen this point, we will be more active in participating in national and international conferences, and in further developing national and international collaborative partnerships.

Finally and as indicated to the committee during the site visit, the present large size of our research group is the result of a deliberate strategy to provide our team most of the expertise required to successfully fulfill our future project with every of the senior scientists involved in most of our research projects. We will work in this format for the next 4 years. However, during this period (2011-2014), we will evaluate the opportunity to promote the emergence of a new group.

CRLC Val d'Aurelle Paul Lamarque
Centre Régional de Lutte contre le Cancer
Etablissement de soins certifié H.A.S. en 2007
Etablissement sans tabac, membre du réseau Hôpitaux sans tabac.
Le Directeur Général

Montpellier, le 9 mars 2010

JBD/GD/2010-057

Note sur les relations IRCM / CRLC Val d'Aurelle

Le Centre Régional de Lutte contre le Cancer (CRLC) Val d'Aurelle a créé avec l'Université Montpellier 1 et l'INSERM, l'Institut de Recherche en Cancérologie de Montpellier (IRCM).

Après analyse du rapport préliminaire de l'évaluation AERES de décembre 2009, le CRLC confirme son implication et son soutien à l'IRCM.

- Le soutien financier du CRLC à l'IRCM sera confirmé et même amplifié : hébergement, soutien aux dépenses de structure, soutien aux dépenses d'une partie du personnel technique et des ingénieurs de recherche, soutien à certains équipements et plateformes technologiques.
- En réponse aux difficultés mentionnées par le comité AERES concernant la connexion de l'IRCM avec les laboratoires d'anatomopathologie et de biologie moléculaire de routine, le CRLC a mis en place dès janvier 2010 un comité de coordination de la recherche translationnelle. Place sous la direction d'un PU-PH du CRLC, ce comité regroupe les responsables de l'ensemble des plateaux techniques du CRLC (anatomo-pathologie, biologie spécialisée, pharmacie), le directeur et le directeur-adjoint de l'IRCM. L'objectif de ce comité, qui préfigure une future plateforme commune CRLC-IRCM, est d'assurer une utilisation optimale des ressources biologiques du CRLC et de favoriser leur utilisation par les équipes de l'IRCM.
- L'arrivée d'un nouveau responsable de l'unité de biostatistiques du CRLC en juin 2010 constitue une opportunité de réponse à une des critiques du comité AERES concernant la bioinformatique. En effet, le candidat sélectionné par le CRLC pour ce poste possède une reconnaissance internationale en bioinformatique. Le CRLC s'engage à impliquer cette nouvelle personne au sein de l'IRCM.

Professeur Jean-Bernard DUBOIS,

Directeur Général

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Établissement de soins à but non lucratif, réalisant un service public hospitalier, reconnu d'utilité publique