Oncogénèse et progression tumorale

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Centre de Recherche en Cancérologie de Lyon

From the

University Lyon 1

CNRS

INSERM

May 2010

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Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

May 2010

Research Unit

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

Requested label : UMR CNRS, UMR_S INSERM

N° in the case of renewal

Name of the director : M. Alain PUISIEUX

Members of the review committee

Chairperson :

M. Daniel OLIVE, Marseille

Other committee members :

M. Aristidis MOUSTAKAS, Ludwig Institute for Cancer Research, Uppsala, Sweden

M. François REZVANI, Institut Curie, Paris

M. Gilles PAGES, Université de Nice-Sophia Antipolis

M. Jacques BERTOGLIO, Université Paris 11

M. Jean François DUFOUR, University of Berne, Switzerland

M. Michel RIGOULET, Université Bordeaux 2

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M. Peter JORDAN, Instituto Nacional Ricardo Jorge, Lisboa, Portugal

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

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Research Organization representatives :

Mrs. Evelyne JOUVIN-MARCHE, CNRS

Mrs. Chantal LASSERRE, INSERM

Report

1 • Introduction

- Date and execution of the visit

The visit took place on January 27th and 28th, 2010 at the Centre Léon Bérard (CLB). The project was presented by the future director. Then the Department, Platform and Team representative leaders presented their projects. After separate meeting with the PhDs, post docs, researchers, and technicians, the Committee had a discussion with the representatives of University of Lyon 1, Centre Léon Bérard and the DRC of Hospices Civils de Lyon. Then, a final meeting with both the future director and the department and team leaders was followed by a closed-door meeting of the committee. The presentations of the teams from Departments 1 and 2 were organized into two parallel sub-committees, with the opportunity to listen to team leaders as well as junior scientists. There were thorough and extensive discussions on most aspects of the projects as well as the management of the research and its integration within the Lyon-Est research campus.

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

The project of creating the Centre de Recherche en Cancérologie de Lyon (Lyon Cancer Research Center) is dedicated at constituting a Center of Excellence in cancer research in Lyon, with a strong potential for medical application, and to facilitate the transfer of knowledge to clinical applications in oncology. The initial decision originates from a strong will of the different participating teams to gather their expertises for better cooperation.

The project corresponds to the association of INSERM, CNRS and University units located on the Lyon-Est site, which are dedicated to cancer research (INSERM Unit 590; UMR-CNRS 5238; UMR-CNRS 5201; INSERM Unit 865, and INSERM Unit 871). These teams are located at the Centre Régional de Lutte contre le Cancer (Léon Bérard Regional Cancer Center), the Édouard Herriot hospital (Hospices Civils de Lyon), the faculties of Medicine and Pharmacy of the Université Claude Bernard Lyon 1, and nearby Inserm building. It is important to emphasize that the project is not just a juxtaposition of pre-existing units and teams, but rather arises from profound and thoughtful rearrangements among teams, such as splitting a Unit into two different teams, gathering two groups into one team, and creating new teams by individualization of smaller groups.

The project includes a total of 19 teams organized into 3 departments, which share common priority research themes such as 1) The study of mechanisms of tumoral escape ; 2) The analysis of mechanisms of avoiding immuno-surveillance; 3) Analysis of the perversion of information flow by the carcinogenic process.

- Management team

The CRCL is managed by a Director, assisted by an Executive Board and a Management Committee. The Director is in charge of the general administration of the Center and its external representation. He chairs the Executive Board which associates the Department Heads every month. This board takes decisions on all issues related to the organization and changes affecting the Center, including the global strategy of the Center. The Management Committee examines directions taken and the implementation of the Center's policy in all its scientific, administrative and management aspects, including shared premises and services.

- 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)	46	44
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	46	44
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	68	49
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	34	33
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	41	36
N6: Number of Ph.D. students (Form 2.7 of the application file)	83	46
N7: Number of staff members with a HDR or a similar grade	74	67

*: past, June 2009; future: from January 2010

2 • Overall appreciation on the research unit

- Overall opinion

The Centre de Recherche en Cancérologie de Lyon submits a very ambitious project that associates existing INSERM and CNRS units devoted to the field of cancer and chronic viral infections. The final objective is the creation of an excellence center on Cancer gathering most research labs from Lyon-Est. The project is the logical outcome of the previous efforts made by CLB, AP-HL and the University together with Canceropole CLARA and the RTRS Lyon Synergie Cancer. The final project associates 19 teams within three departments localized on different but close sites (CLB, Edouard Herriot, Faculté de Médecine et Pharmacie, Inserm building). The size of the center prompted to propose to associate to the Director an Executive committee with the Department heads that will have to coordinate the projects and help developing the research topics within the different sites and areas of research. The management of the structure and the development and efficiency of the platforms will be major issues that will have to be tackled during the next four years in order to fully succeed. The research areas developed by the different team leaders are important in the field of cancer and chronic viral infection and they present numerous complementary aspects that foster internal collaborations. The overall structure has convincing potential, with a number of excellent research teams either on basic or translational research and importantly, some outstanding teams that should help to further improve the overall quality of the Center and drive its external visibility.

- Strengths and opportunities

- Excellent synergy for developing cancer research associating research organizations, the University and the hospitals ;
- The participation of internationally-recognized teams in both basic and clinical research in oncology and viral infection warrants the quality of the future Center ;
- The participating teams show a strong will to create this joint project and to build a Center through major reorganization of previous laboratories. Altogether, the three departments and most teams are convincing and will give a major added value.
- Opportunity is given to young investigators (ERC, AVENIR-ATIP) to be team leaders ;

- The close proximity of highly developed medical facilities in the area of oncology (Centre de Lutte contre le Cancer Léon Bérard and Édouard Herriot hospital), of the faculty of medicine, the involvement of clinicians, pathologists and MD-PhD students and their association with a CRB provides opportunities to foster translational research ;

- The availability of large research spaces in the different sites and especially on the CLB will allow to further develop the project.

• Weaknesses and threats

- The ability to coordinate the projects on the different sites and to associate the previous INSERM and CNRS labs for developing new projects will be mandatory ;

- It will be important to develop an oncology research training to attract students and afford them a training in oncology ;

- There is need to develop up-to-date platforms ;

- An administrative structure that will support the center has to be created.

• Recommendations to the head of the research unit

The future director should define deliverables regarding administrative structure and platforms. It is mandatory to favour the interactions between teams and departments to avoid dispersion and continue the high quality research performed in the different teams of the future center.

• 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	86
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	48
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	0.97
A4: Number of HDR granted during the past 4 years	21
A5: Number of PhD granted during the past 4 years	64

3 • Specific comments on the research unit

• Appreciation on the results

Most of the teams develop either excellent or outstanding research projects relevant for cancer and chronic viral infection. For instance, the recent discoveries dedicated to cancer development and viral infection look promising. Among others one can highlight the role of TWIST genes in cancer development, identification of TLR3 and MyD88 as apoptosis inducers in cancer, role of TGF-beta in autoimmune development in mice, and mutations of ALK tyrosine kinase in neuroblastoma.

The number and quality of the publications is impressive and in general excellent including 123 articles with IF>10.

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

The members of this unit have obtained numerous prizes and distinctions including awards from the Académie des Sciences, Eurocancer, Raymond Rosen.

The Center has been very active in recruiting young scientists new team leaders or researchers from France or abroad.

The teams have been very efficient at raising funds. Most of them are involved in networks with the industrial clusters as well as Canceropole and RTRS.

Several PIs are associated or coordinators of international and national networks such as the Virgil Network of excellence of EU, and EORTC.

Most teams are tightly connected with Canceropole as well as Lyon Biopole and Lyon Synergie Cancer.

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

The project presented should allow to obtain an excellent governance based upon the existence of committees, departments, international scientific board and an administrative unit.

The scientific projects will be coordinated at the level of the Departments. Risky projects might develop thanks to the existence of pre-existing top levels teams that will help developing the new projects.

Assistant Professors and Professors are in charge of teaching responsibilities in master's degree training and occasionally of teaching units in the M1 and M2R. The teachers are active both at the Science Faculty as well as the medical and pharmacy schools.

- Appreciation on the project

The overall projects can be summarized according to the titles of three departments 1) The study of mechanisms of tumoral escape ; 2)The analysis of mechanisms of avoiding immuno-surveillance; 3) Analysis of the perversion of information flow by the carcinogenic process. In general, the projects are either ongoing projects that were already fruitful and will expand or some new and risky projects that in most instances are excellent. The advantage of the creation of departments is the ability to support emerging teams as well as risky projects. It has to be noted a major reorganization of the previous units that allowed to associate new and emerging teams within departments through extensive teams reorganization (for instance teams E2, E16, E17, E18, E19). Among others, this reorganization permits to propose projects that are between innate immunity and virology (E13, E14 and E17) and innate immunity and therapeutic mAbs (E13 and E16), to develop integrated projects on TGF-beta signaling (from mouse models of cancer to NKT cells).

In most instances the projects are original with some being risky. One of the major advantages of the proposed structure is the ability to support risky projects thanks to the pooling of all the resources. The budget obtained by the teams will be allocated to the CRLC and a percentage will be given to the Departments that will use it for platform development and funding selected projects.

4 • Appreciation team by team

E1 Team: Apoptosis, cancer and development

Team leader: M. Patrick MEHLEN

- 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)	10	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	4	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	7	3
N7: Number of staff members with a HDR or a similar grade	2	2

- Assessment of work produced and scientific quality:

This team represents a leading group worldwide on dependence receptors. The PI has discovered the concept while in a postdoctoral position and he is developing this theme of research in his team, not only in the field of cancerology but also in other fields, like neurobiology.

The level of publications is outstanding. The team has published 43 papers during the last 5 years including 10 with IF>10 (2 Nature, 4 Nature Cell Biology, 1 Nature Review Cancer, 1 Dev Cell., 1 JNCI, 1 J Exp. Med., and 1 EMBO J. 5 PNAS, 2 Mol. Cell. Biol., 2 Cell Death Differ). Among these papers, 10 correspond to reviews and 10 to collaborations.

Also 8 patents have been filed; one Start-up company has been launched in 2008.

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

This team shows a very good integration within the Centre, several teams of the centre especially teams E2, E3 and E5 are collaborating with the team.

The PI won numerous French awards. Internationally, the team leader was elected member of EMBO and has been named adjunct professor of the Buck Institute for Age Research (Novato, California). Several other members of the team have obtained different French awards.

The laboratory has hosted post-docs from Portugal, Italy, Spain, Mexico, Romania.

The team obtained grants from INCA, Ligue Contre le Cancer, RTRS, CLARA.

The quality of communication is very good as evidenced by the number of prizes and distinctions and the involvement of the PI and team members in scientific committees.

Several ongoing collaborations with French and foreign teams within European projects are listed. One can quote international leader teams in the University of Lausanne, Norfolk University, and in Sanford-Burnham Medical Research Institute, La Jolla.

Several patents have been obtained. There is a spin off company that was created from the work of the group.

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

The initiatives aimed at scientific coordination, emergence of cutting edge projects and taking of risks are very good and is exemplified by launching the Netris Pharma.

Strong involvement of several team members in educational activities has been noted.

- Appreciation on the project

Ten years ago, the team leader put forward the new concept of dependence receptors (DR) whereby these receptors do actively induce cell death in the absence of their cognate ligand. The program of the team has been, and will be, focused on the understanding of the intracellular signalling leading to apoptosis induction under these conditions.

Importantly, this concept is also being extended, as these DR might function as tumor suppressors, opening new areas of research that may contribute to cancer therapy :

- Part 1: Cell signaling downstream of dependence receptors and mechanisms of caspase activation ;
- Part 2: Role of dependence receptor-induced apoptosis in development of the nervous system; this aim makes use of original animal models ;
- Part 3: Role of DCC, UNC5H and Ptc pro-apoptotic activities in the regulation of cancer progression and metastasis. This part will investigate whether DR mutations can be detected in human tumors and attempt at interfering with ligand receptor interactions.

The project is very clear, logical and it seems that it can be performed in a reasonable time frame.

The field of dependence receptors is rather new. The different projects are not risky and despite this, should lead to interesting and important results.

- Conclusion

– Overall appreciation

This is an excellent team with high international visibility. The project is very interesting and the team is efficient.

– Strengths and opportunities

This highly productive team works on an interesting field with a clear relevance for cancer.

– Weaknesses and threats

It is a very large group. The direction of a large group together with all the activities of the team leader may become a tour de force if not relying on “subgroups leaders” who are not identified. This could be a potential problem.

In spite of having 8 engineers, technical and administrative staff, this team does not benefit from an administrative assistant with a tenured position.

E2 Team: Escape from failsafe programs and cellular plasticity

Team leaders: M. Alain PUISIEUX and M. Stéphane ANSIEAU

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

	In the report	In the project
N1: Number of professors (see Form 2.1 of the unit's dossier)	4	4
N2: Number of EPST or EPIC, researchers (see Form 2.3 of the unit's dossier)	2	1
N3: Number of other professors and researchers (see Form 2.2 and 2.4 of the unit's dossier)	5	3
N4: Number of engineers, technicians and tenured administrative staff members (see Form 2.5 of the unit's dossier)	4	0
N5: Number of engineers, technicians and non-tenured administrative staff members (see Form 2.6 of the unit's dossier)	3	2
N6: Number of doctoral students (see Form 2.8 of the report unit's dossier and 2.7 of the project unit's dossier)	6	1
N7: Number of persons accredited to supervise research and similar	6	5

NB: The E2 team has a new structure: the former group now joins the E19 team while the E2 team has also been reinforced with the arrival of new members.

- Assessment of work produced and scientific quality:

The research performed over the past 5 years by the E2 team is world-class and well respected by the fields of cancer research and EMT internationally. Three different aspects have been developed, including inter-regulation of p53 family members, oncogenic activation of TWIST and p53 inactivation, and p53 responses to genotoxic stress. While two of these themes have allowed to better understand the regulation and functional impact of p53 family members in different cancer types, one of the approaches taken by the E2 team has proven rather unique as it focuses on mechanisms of regulation of tumor cell senescence. This research led to the recent concept that molecular factors that were previously known to drive the process of EMT are also capable of controlling the self-renewing capacity of cancer stem cells at least in breast cancer. This finding has opened vast new areas of modern cancer research. The quality is superb and the impact is profound. Other themes developed by a second group of the team have given rise to very good.

The E2 team publishes regularly at the leading journals of cancer research and the work of the team has been praised internationally by commentaries written by the very top scientists in the field. The numbers of papers published and accompanying doctoral theses are exemplary. The team has published a total of 48 original articles during the last 5 years, including 28 papers signed in first or last position by a member of the team in excellent and occasionally in top-level journals (Cancer Cell), 20 papers in collaboration, sometimes with other teams of the center (Nature, J Exp Med, Nat immunol, Hum Mutat), and 23 reviews in high impact journals such as Nat Rev Cancer as well as in other national or international journals.

The E2 team appears to be very well established in the biomedical community of Lyon. It is no doubt that the choice of the E2 leader to also lead the combined effort of this inter-institutional project is well justified.

- Assessment of the influence, appeal and integration of the team or the project in its environment:

The team leader has recently received 2 awards, one national and one at the European level (Raymond Rosen Award and Eurocancer 2009 award). The team leaders have been invited to 13 scientific events nationally and internationally (AACR, 8th conference of International Institute of Anti-Cancer research).

The team shows a very good capacity to recruit good scientists, but it could be even stronger based on the impact of the research of the team.

The ability to obtain external funding is very good, although better success at the international (European level) would be recommended.

Participation to different programs and collaborations are very good. Many such collaborations are already established and with proven effectiveness in terms of publication.

- Assessment of the strategy, governance and life of the team or project:

The relevance of its organization, quality of its governance and internal and external communication is very good. The team leaders have complementary know-how and their external visibility is rewarded by their involvement in scientific committees (ARC, INCA).

The relevance of initiatives aimed at scientific coordination and the emergence and taking of risks is very strong as demonstrated by recent scientific projects analyzing the role of TWIST.

Team members are involved in the teaching of Masters and PhD and they work in the scientific committees of CLARA and RTRS.

- Project assessment:

The project is state-of-the art and leading edge. It is feasible and also promoting future important discoveries.

The project has very high level of originality, as it will now challenge the role of TWIST in EMT and the development of cancer stem cells. Such project has inherent risk-taking but it stems from solid preliminary data.

- Conclusion:

Very positive mention is attributed to this team. A very good program focused on the role of re-programming of epithelial cells via EMT by transcription factors. Proof of concept has been made with the Twist family and will continue with other TF. There is a lot to uncover here. The work is cleverly based on cellular AND animal models AND human samples. The interesting questions nicely deal with several important aspects of oncogenesis, stem cells and programming. The committee gives a particular mention to the well-designed project on circulating cells. Overall, this is an excellent team with an excellent program

– Strengths and opportunities

Multiple strengths and opportunities are evident such as the originality of the TWIST project, efficient governance of the team, involvement of the team in the overall development of the center, collaborations with research labs within CLARA, and with worldwide impact publications and new concepts.

– Weaknesses and threats

The number of foreign scientists and students, and international grants could be improved.

– Recommendations

The team should recruit more foreigners, and obtain more international grants.

E3 Team: Senescent Escape Mechanisms

Team leader: M. David BERNARD

- Staff members

	past	future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	0
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	1
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

The field of senescence is active. The science performed by this team during the past two years (due to the recent recruitment of the team leader) is of very good overall quality taking into account the small size of the group. More specifically, using a functional genetic screen with a retroviral Sh-RNA library, this team has made original and important contributions by identifying some new genes involved in senescence occurrence, including topoisomerase 1, AMPK-related kinase 5 and PLA2R. These elements attested of the great dynamism of this young group leader.

The overall publication record is of high quality with very good princeps publications from the team leader in Cancer Res and EMBO Rep in 2009. He has published high impact factor papers including Cell Nature and EmboJ as co-author, and recent paper as last author in The Embo Journal, The Embo Rep and Cancer Res. He has a very good track record.

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

So far, prizes and invitations to conferences are very limited.

The critical mass was not obvious in the document but the PI has detailed during the oral presentation his project to recruit 2 Post-docs and 1 PhD student.

The PI showed great competencies in obtaining national funding from ARC, FRM, LNCC, BQR (a regional Foundation), amounts are 30-50 k€ per grant, average 80 k€ per year ; an important grant has been obtained from Synergy Lyon Cancer Foundation in 2009 (180,000 euros).

Several ongoing collaborations with French and foreign teams, specifically with the Institute of Biomedical Investigations of Bellvitge (IDIBELL) at the university of Barcelona.

One patent has been filed.

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

Small young team on well focused topic recently coming from Lille through a RTRS junior package. Their project should further foster the collaborative research within the tumor escape department.

- Appreciation on the project

The research program focuses on replicative and oncogene-induced senescence. The two aspects of the research are quite interesting and the technological strategies including screening and animal models are coherent and pertinent. Although similar approaches are being pursued by other teams, the recent results of the laboratory have proven as it is still fruitful. The beginning of the project is straightforward with a technology already in hands in the laboratory. The last part of the project is much less explained (see II 1/c, II 1/d).

Although the proposal is in direct line with the previous one, a new aspect dealing with oncogene-induced senescence (OIS) will be explored. The opportunity to develop this new aspect is well explained, logical and pertinent. The main objectives of this project are:

- Characterization of new genes involved in the escape of replicative senescence. This part includes a study of the p53 and Rb pathways, the search for targets and the study of the more pertinent genes during tumor development (Sh-RNA strategies / cooperation with other genetic events including Ras expression, small T antigen).

- A new aspect will be developed concerning the identification and characterization of genes involved in OIS using immortalized HMEC cells (hTert) expressing an inducing MEK protein upon tamoxifen treatment and loss of function screen with RNAi pools. Genes of interest will be validated by constructing transgenic animals.

- Conclusion

– Overall appreciation

This is a coherent, pertinent and attractive project. The two aspects are well focused and as such will have an excellent feasibility. It is to be hoped that this small team will benefit from the recruitment of one post-doc and one or two PhD students. The record of previous publications is very good taking into account the small size of the team. This small team, already productive, was originally in Lille. The change of environment should be very fruitful.

– Strengths and opportunities

The team has made very good earlier contributions in the field. It presents an Interesting and well focused research program. The PI identified genes that might be relevant for escape from senescence such as Topoisomerase 1 and M type receptor PLA2R. The dynamism of the young team leader has to be highlighted. An excellent network of national and international collaborations has been built. The integration of the team at the CLB (environment, collaborations, platforms) is an excellent opportunity to enhance the quality of research. Team's activities have clear relevance for cancer. The team is likely to bring new ideas into the Department.

– Weaknesses and threats

The current size of the team is too small and lacks PhD and Post-docs. To face competition in the field it will be necessary to increase the critical mass. The part devoted to the characterization of the identified genes is much less clear and should be more precisely defined.

– Recommendations

- Secure some PhD students, at least one post-doctoral fellow and a technician;
- Continue to develop appropriate murine models (in collaboration with other teams of the institute) and estimate clearly the amount of work with the mouse models;
- Clarify the last part of the project.

E4 Team: Epigenetic Alterations and Tumor Escape Mechanisms

Team leader: M. Robert DANTE

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

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0
N6: Number of Ph.D. students (Form 2.8 of the application file)	2
N7: Number of staff members with a HDR or a similar grade	3

- Appreciation on the results

The group was previously integrated into the Pharmacogenomics unit. It has found that methyl-CpG binding proteins like MBD2 mediate the epigenetic transcriptional silencing. A significant finding was that MBD2 acts upon methylated promoters of a specific subset of target genes. This analysis has been extended to genome-wide studies using state-of-the-art promoter arrays representing 25 000 putative human promoter regions (ChIP on chip).

One work in progress should give a very interesting paper.

Three publications are listed as a first or last author from members of the group. The group has produced roughly one paper each year in a good international journal (Oncogene, NAR). (Information was taken from the IF of the team leader because it is missing in the printed report from group 4 (Bilan, pp 93-106), in particular the two reported publications with IF>20 were not found). Good publications, some in collaboration with a group leader in the field of epigenetics.

Two papers were published in Oncogene in collaboration with a Spanish group well recognized in the field.

A collaboration with a top researcher in the epigenetic field led to joint papers; no information is given regarding the continuation of this joined work. The local partnership with the head of the genomic core facility profileXpert was fruitful.

- 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 the sole team working on epigenetics in the Centre. It should be noted that one of the members of the group is responsible of a functional genomic and high-throughput sequencing platform

It seems that the team has difficulty to recruit post doc and students.

Funding has been obtained by two national grants (INCA, PHRC) and one application has been submitted to ANR with two recognized researchers in the field.

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

The collaboration with the genomic core facility profileXpert has been strengthened, leading to its integration into the team E4 that is programmed in 2011.

The team has set up ChIP on chip analysis using promoter arrays.

In the past, teaching activity was mostly restricted to PhD student orientation. The proposed new unit E4 will integrate four members involved in teaching.

- Appreciation on the project

The group has set up Chip-on-chip analysis to identify the presence of mCpG binding proteins at specific gene promoters and will apply this technique to additional cellular models or patient samples, which are recruited from within the Center in Lyon. The project is relevant to identify potential tumour suppressor genes and the team has sufficient experience in this field.

The project is well structured and is backed by high quality platforms (Platform IBISA "functional genomic and high throughput sequencing" and collection of brain tumors or cervical). Mention is made of an original cellular model consisting of mammary epithelial cells transformed by the protocol of Weinberg, in which changes in the profiles of methylation and MBD protein binding are made. Some more will be done on clinical samples of cancer with the platforms above. Another part of the functional role of MBD2 in xenotransplantation will be performed. There is no mention of a "schedule" in terms of objectives.

Although of potential interest, description of the project is too short, very vague in some parts (what type of experiments will be done on the human samples for example). There are not enough connection between the cellular models (breast, keratinocytes) and the human tumours (from pituitary and cervix). Concerning the part on the dependence receptors, it is likely that MBD2 inhibition will induce the reexpression of many genes that not only belong to the dependence receptor family and therefore the results of the in vitro experiments targeting MBD2 by siRNA in presence of dependence receptor ligands with will be crucial before going further.

The project will exploit the technology previously established in the group to analyse novel types of tumor models or samples. Originality is linked to cellular models (transformed mammary cells) and attempted treatment in preclinical studies with siRNA. However, this strategy has been poorly efficient previously. The partial hydatiform moles (PHM) model is also very original for the study of loss of cell growth control and altered differentiation with hypomethylation of repetitive sequences.

- Conclusion

The study of epigenetic modifications that contribute to tumourigenesis is an important field and the group builds on its previous finding that the MBD2 protein binds to methylated promoters. This know-how will be employed to analyse novel cancer cell models apparently provided by other groups from the CRC Lyon or by the recently integrated staff researchers. In addition, the proposed downregulation of MBD2 in various models should validate its role in tumour suppression. This group is important for the center for two reasons : one member of the team is responsible for a platform potentially very useful fo the centre, epigenetics inactivation is an important mechanism in cancer and there is only this group working on epigenetics. However the project is not in the present form completely convincing.

– Strengths and opportunities

The group has passed to genome wide studies using promoter arrays and integrated the researchers in charge of the genomic profileXpert service platform. Collaborations were trained to study epigenetic silencing of Dependence Receptors, including xenograft mouse models. Strong collaboration has been established with an internationally recognised group in the field of cancer epigenetics. One of the members of the group is responsible of the functional genomic and high-throughput sequencing platform.

– Weaknesses and threats

No recruitment of Post-docs for bench research and no technician are planned. The integration of two staff researchers without expertise in the epigenetic field increases the team size with no obvious advantage. The ratio between researchers and part time researchers is relatively low, which can lead to a lack of competiveness.

Proposed range of tumour types or cancer cell models can lead to dispersion of activities. The project has not been perceived to be convincing.

– Recommendations

Epigenetic is important for cancer and this is the only team addressing this issue. However, in its present form the structure of the team does not seem to be viable as an independent team to achieve the project. The committee has doubt about the competitiveness of the group without additional expertise for example recruitment of other teams working on epigenetic modifications.

E5 Team: Endocrine differentiation: interactions with tumorigenesis and tumor progression

Team leaders: M. Jean-Yves SCOAZEC and Chang-Xian Zhang

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

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	8
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	7
N3: Number of other researchers including postdoctoral fellows (Form 2.2, 2.4 and 2.7 of the application file)	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	8
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0
N6: Number of Ph.D. students (Form 2.8 of the application file)	3
N7: Number of staff members with a HDR or a similar grade	8

- Appreciation on the results

The E5 team results from the fusion of the Inserm U865 unit (a), a team from UMR5201 CNRS unit, “Biology of MEN-1” (b), and a group from INSERM U664, “Functional genomics of thyroid cancers and their metastases” (c).

The first group (a) studies mechanisms of tumor initiation and progression in gastroenteropancreatic endocrine tumors, using experimental in vivo and in vitro approaches with a clinical interface. Main results obtained in the last 4 years include the identification of interactions of the tumor-suppressor gene product MENIN with the NF-KB and p53 pathways in endocrine cell lines, and the finding that beta-catenin mutations are restricted to a subgroup of aggressive endocrine tumors. In addition, the team made the original observation that, in contrast to other epithelial tumors, benign endocrine tumors are more vascularized than gastroenteropancreatic malignant tumors, which could have potential impact on the identification of new prognostic markers and new therapeutic strategies.

The second group (b) has generated mouse lines with conventional and conditional knockout targeting the MENIN1 gene. The MENIN1 KO proved to recapitulate the MEN1 pathology characterized by multiple endocrine tumours. The group is currently exploiting the conditional KO to better refine their studies on MEN1 pathology and to explore the different types of tumours developed in Men1 mutant mice. These KO models are also used to decipher the role of MENIN1 in the normal development of endocrine tissues.

The past activity of the third group (c) was not provided in the AERES « Bilan » document, because people come from another structure not involved in the CRCL project (INSERM U664).

Numerous papers have been published around the three topics previously developed including 2 Gastroenterology, 1 PNAS and 1 Oncogene. The IF of others do not exceed 5.

Publications from group (a) include 48 publications, of which 22 are signed by at least one member of the team as first or last corresponding author, and 26 are from collaborative work.

Publications from group (b) include 26 publications, of which 10 are signed by at least one member of the team as first or last corresponding author, 13 are from collaborative work, and 3 correspond to previous post-doctoral work abroad. Of note, one of the team members signed 10 publications alone in the quadrennial with no apparent link with the team. Is there a planned integration in the new team?

Publications from group (c) include 23 publications, of which 8 are signed by at least one member of the team as first or last corresponding author.

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

Good recruitment of staff scientists from INSERM and University should be noted, but only very few Post-Docs.

Funding of the projects appears ensured by several LNCC and ARC grants. One of the group leaders is the coordinator of an ARC-INCa grant. No international funding mentioned.

The two group leaders are frequently invited as speakers in conferences, mostly in France.

Very good collaborations with the Centre Européen de RMN, Carte d’identitié des Tumeurs (LNCC), CEA and IARC.

Very good results are evidenced by the development of important animal models as well an excellent ability to collect the samples and relevant informations on these rare tumors.

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

Since this is a newly formed structure, the functioning and the management are quite difficult to assess.

The question of leadership of the former group leaders is raised.

One of the proposed group leaders is the present Director of INSERM UMR 865 until January 2011 and future deputy Coordinator of Department “Tumoral Escape”.

The future team will be very large in size (more than 20 permanent positions) raising the risks of difficulties in its management as well as of poor interactions with other teams in the department.

The new team will be codirected by two team leaders who have for one an excellent expertise in clinical research and for the other an excellent knowhow in the development of animal models. This association could help to tackle the understanding of endocrine tumor emergence and metastasis.

All the University Professors and Assistant Professors have regular teaching activities in Faculty of Medicine, at both the undergraduate and graduate levels: 8 PhDs have been defended during the last 4 years.

- Appreciation on the project

Within the frame of the future CRCL, the newly composed team will continue to use endocrine tumor models to explore how the maintenance of a specific differentiation program influences the balance between proliferation, differentiation and apoptosis and the interactions between tumor cells and their microenvironment during tumorigenesis, including tumor initiation and tumor progression.

Three main themes will be addressed by combining in vivo and in vitro experimental approaches with a strong clinical interface:

The analysis of the mechanisms of tumor initiation and early progression, through the study of the MEN-1 gene

The mechanisms of late progression, including the specific role of angiogenesis in these processes.

The identification and validation of biomarkers and therapeutic targets through large scale analytic technologies.

The project is highly interesting and displays strong assets. Putting together the different research teams working on endocrine tumors in Lyon should result in a strong potential.

However, although important effort was made to integrate the fusion of the three groups, this results in a sometimes superficial description of the future projects. For example, only an overview of the third theme is summarized, but details and feasibility of the projects are not provided. In addition, there is no systematic overlap between the projects described in the independent teams’ “bilan” and those described in the “project”.

The project on the angiogenic potency of endocrine tumors that behave differently compared to other tumors is very original. To go against the general dogma is risky but could represent a breakthrough in the field of angiogenesis.

- Overall appreciation
  - Strengths and opportunities

A major strength is to put together the research teams working on endocrine tumors in Lyon. The group leader and future deputy director of the department has already developed for several years an impressive number of collaborative projects with many different teams of the future CRCL.

The groups have strong clinical connections (Hospices Civils de Lyon) : the team has set up a translational research continuum between human tumor tissue facilities and basic research.

– Weaknesses and threats

This is a very large team with 16 ETP staff scientists (1DR, 7CR, 4/5PU-PH, 5MCU) …… and 7 ITAs (ETP).

A whole INSERM unit is incorporated into the team. The leadership might be difficult to achieve with multiple projects to coordinate, although enough FTE are available.

At least 10 distinct objectives are defined in the proposal! Although an important effort was made to integrate the fusion of the three groups, this results in a sometime imprecise description of the future projects.

The biomarker part is not convincing. The team should take better advantage of the animal models they have or develop new ones.

– Recommendations

The team leaders should try to find leading projects which integrate the different expertises of the teams and if possible define a common theme to increase the international visibility of the team.

E6 Team: Role of TGF-beta in Pancreatic and Gastrointestinal Cancers

Team leader: M. Laurent BARTHOLIN

- Staff members

	In the report	In the project
N1: Number of professors (see Form 2.1 of the unit's dossier)	0	0
N2: Number of EPST, *Établissement public à caractère scientifique et technologique* (Public scientific and technological institution) or EPIC, *Établissement public à caractère industriel et commercial* (Public industrial and commercial institution) researchers (see Form 2.3 of the unit's dossier)	0	1
N3: Number of other professors and researchers (see Form 2.2 and 2.4 of the unit's dossier)	2	2
N4: Number of engineers, technicians and tenured administrative staff members (see Form 2.5 of the unit's dossier)	0	0
N5: Number of engineers, technicians and non-tenured administrative staff members (see Form 2.6 of the unit's dossier)	2	2
N6: Number of doctoral students (see Form 2.8 of the report unit's dossier and 2.7 of the project unit's dossier)	1	1
N7: Number of persons accredited to supervise research and similar	0	0

- Assessment of work produced and scientific quality:

The research performed over the past 5 years by the E6 team is promising and has already led to significant results. The group is still young. The area of research, pancreatic cancer and TGF-beta signal transduction is very relevant and is worth promoting in the future. This is based on the low effectiveness in treating pancreatic cancer patients.

New genetic mouse models have been established to understand the dual role of TGF-ß in growth inhibition or tumor progression, including knock-in models for activated TGF-ß RI receptor and knock out of TIF1g, both focussing on pancreatic cancer Although the team is young the productivity has started showing up.

Very promising publication record with 3 papers during the two year period of existence of this young group. During the 4 years, the PI has published 7 papers as 1st author, 1 as last and 3 collaborations.

The PI has been invited to the FASEB conference

The E6 team seems to be well established but requires more time to prove its impact locally, nationally and internationally. However, the local collaborations have been productive since 4 publications have been published. National collaborations are too early for productivity. International collaborations are with the post doctoral laboratory (2)

Stable local and national contacts have been established ; clear orientation of the PI towards partnerships has been noted.

- Assessment of the influence, appeal and integration of the team or the project in its environment:

Attribution of an Avenir award to the PI. The team leader has not yet shown other distinctions.

This is still a small team but with good potential for the future.

The ability to recruit top-level scientists is not applicable considering the two year period of existence of this young group which is currently trying to expand. They have recruited one post-doc, one engineer and one PhD student.

The team requires better funding prospects for the future.

The team has engaged important national and international collaborations, particularly with the Department of Molecular Biology, Massachusetts General Hospital, Boston, some of which have already given positive results. In addition, the project should be complementary to that of other groups of the CRLC (teams E3, E15).

- Assessment of the strategy, governance and life of the team or project:

The PI is definitely a “group leader”. He is very enthusiastic with strong determination and able to define priorities for his projects.

Good initiatives are taken as the team focuses on pancreatic cancer in mouse models, a very difficult area of cancer research and a very competitive area. The PI decided to explore a very interesting idea generalized by top leaders in the TGF-ß field, and he generated mouse models to test this idea in the pancreatic cancer field. This is very original. The basic idea behind this project is published by two very strong international groups from New York and from Padua. These groups generated models with incompatible mechanisms that aim to explain how TIF1γ regulates TGF-ß/Smad signaling in vitro and in vivo. The E6 team has now taken the important task to explain the discrepancies and provide a definitive mechanism of action of TIF1γ using transgenic mouse models with TIF1γ or TGF-ß/Smad mutations engineered to be expressed specifically in the pancreas of the mice. This approach is pioneering and promises to resolve the current discrepancies in this field. The TGF beta domain is very competitive but the PI’s intelligence was to concentrate his efforts on the pancreatic cancers. He has developed very original mouse models. These animal models represent a really important breakthrough in the field for testing therapeutic agents.

Teaching duties are limited to supervision of a PhD student.

- Project assessment:

The project is state-of-the art and leading edge. The research program is difficult but well planned and feasible and also promoting future important discoveries. He has developed an original “ecological niche” in the domain of pancreatic cancer.

The proposed research is relevant given the poorly understood dual role of TGF-ß in growth inhibition or tumor progression. The work is a continuation of a recent research line on pancreatic cancer and is feasible due to the mouse models meanwhile created. The long-term transfer of the know-how and mouse model approach to gastrointestinal cancers is relevant and convincing. These transgenic mice also provide potentially useful in vivo models to test the effect of TGF-ß inhibitors.

The PI has a clear idea about the required financial support and is applying for external funding.

The mouse models for pancreatic adenocarcinomas and pancreatitis established by this group are rare. The investment to develop further mouse models to activate TGF-b RI in the gastrointestine is also unique. PI makes active attempts to coordinate research with other leading labs in the field and avoid overlaps and competition.

- Conclusion:
  - Opinion:

This is a very promising and dynamic research proposal based on original and newly created mouse models. Within the two year period of existence of this young group, the results produced give credit to its feasibility.

  - Strengths and opportunities:

Original mouse models were created. Dynamic and multi-disciplinary approaches are developed to study the role of TGF-b and evaluate the potential of mouse models to test therapeutic interventions.

  - Weaknesses and threats:

Continued financial support and research fellow recruitment are required. The PI has recently obtained a permanent position so he can compete to national grants (ANR, INCA).

The PI should be careful dealing with a lot of mouse models. Funding is essential to maintain different lineages. The team needs to focus on one model as indicated by the PI.

  - Recommendations:

- Follow-up studies on the operating signaling mechanisms should be extended;
- Focus on a restricted number of mouse models is required for better efficiency;
- Apply for external funding.

E7 Team: Early Molecular lesions in Oncogenesis

Team Leader: M. Serge MANIÉ

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

	past	future
N1 : Nombre d'enseignants-chercheurs (cf. Formulaire 2.1 du dossier de l'unité)	0	0
N2 : Nombre de chercheurs des EPST ou EPIC (cf. Formulaire 2.3 du dossier de l'unité)	3	3
N3 : Nombre d'autres enseignants-chercheurs et chercheurs (cf. Formulaire 2.2 et 2.4 du dossier de l'unité)	0	0
N4 : Nombre d'ingénieurs, techniciens et de personnels administratifs titulaires (cf. Formulaire 2.5 du dossier de l'unité)	1	1
N5 : Nombre d'ingénieurs, techniciens et de personnels administratifs non titulaires (cf. Formulaire 2.6 du dossier de l'unité)	0	0
N6 : Nombre de doctorants (cf. Formulaire 2.8 du dossier bilan de l'unité et formulaire 2.7 du dossier projet de l'unité)	3	1
N7 : Nombre de personnes habilitées à diriger des recherches ou assimilées	1	1

- Appreciation on the results

Well-structured project with original data on the basis of cell transformation in multiple endocrine neoplasia type 2A (MEN2A). The original observation is related to the identification of an endoplasmic reticulum stress. If this barrier is lifted tumor transformation is initiated. This also depends on cleavage of CD44 which intracellular part could become a transcriptional activator as in the case of Notch. The identification of target genes is included in the project as well as the generation of transgenic mice expressing the cytoplasmic portion of CD44

This team established an inducible dimerization system of the tyrosine kinase receptor Ret that mimicks MEN2A (Multiple Endocrine Neoplasia type 2A) oncogenic activation. This system relies on the use of a chimeric Ret-Fv protein that can be alternatively activated in the same cell, either with the natural ligand GDNF or with a synthetic bivalent dimerizing ligand (MEN2A-like activation). This model allows the triggering of an oncogenic signaling in a non-transformed cell and the comparison with ligand-inducible signaling. Using it, novel early molecular events induced by oncogenic activation of Ret were identified. One of them (CD44 cleavage) favours cell transformation, while two others appear to constrain it. Thus, recent yet unpublished data from the group suggest that endoplasmic reticulum stress (ERS), by triggering apoptosis, functions as an inhibitor of MEN2A malignancy initiation. In addition, oncogenic activation of Ret induces the cleavage of the adhesion molecule CD44 that releases its intracellular domain (CD44-ICD). Finally, the model allowed identifying a novel endosomal-associated protein implicated in cellular cholesterol homeostasis that possesses oncosuppresive activity. Its expression, which is strongly increased upon cell contact inhibition, is inhibited by oncogenic Ret signalling, suggesting that down-regulation of this molecule is an early event associated with cell transformation.

The scientific production of this small team is of good quality but it has been rather modest these last 4 years: 1 Cancer Res. (7,5); 1 J.Biol.Chem. (5,5); 1 J.Cell.Biol. (2005) (9,1). So far the team leader is first author of 2 papers, 1 as last author and 2 as collaborations. However, new tracks have been outlined and several manuscripts describing these novel findings are currently being submitted. One team member recently recruited has 5 papers as first author mainly during her post-doc, 15 as co-author.

Two PhD theses have been defended. A selected oral presentation at a Gordon Conference merits. The team has made 1 patent application.

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

Recruitment of two full-time researchers over the past two years attests the attractiveness of the team. Good collaborations have been established with other members of the Institute.

Funding was obtained from the League and ARC only.

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

Small team that recently attracted one researcher and hired one researcher. This should allow the development of the proposed projects.

- Appreciation on the project

The project is well described and focused. They have no major competitors on the Ret project.

It is proposed that the cleavage of CD44 following oncogenic Ret activation not only modulates tumor cell adhesion, but also affects early events in tumorigenesis through the nuclear translocation of CD44-ICD. The future projects aim at characterizing the underlying molecular mechanisms of action, notably through a search for specific CD44-ICD partners and target genes. As a long-term project, a transgenic mouse model is also considered. The second part of the project will focus on deciphering the role of ERS as an inhibitor of MEN2A tumour initiation.

The project is scientifically relevant in the MEN2 context that is little studied. The comments are interesting and reflect the maturity of the project in terms of profile evolution of MEN2. The study area is investigated for a long time and has undergone constant evolution. However, a timetable of the targets and deliverables is not given.

Obtaining transgenic mice expressing the intracellular domain of CD44 is original but risky and it is a very expensive project. However, the environment is ideal for developing mouse models.

- Conclusion :

  – Overall appreciation

The team presents a good project, very well focused. The team should continue its efforts to increase manpower.

  – Strengths and opportunities

The team has an original model with statutory dedicated researchers. Excellent opportunities exist in terms of collaborations with other local teams with transgenic animals in which the assumptions could be validated.

The group leader is the scientific coordinator for the axis “Tumor Escape” of the “Cancéropôle Rhône-Alpes Auverge” (CLARA), in charge of helping the emergence of collaborations within this theme.

  – Weaknesses and threats

The work with transgenic animals is very difficult and requires substantial financial resources and management of animal space. It is a risk for a small team with limited resources.

The team has clearly identified itself its own weaknesses and needs: to increase manpower, likely by recruiting post-docs, and funding. The team also needs to improve the publication output.

  – Recommendations

The team could develop a collaborative consortium with the Bordeaux groups on Endoplasmic Reticulum Stress.

E8 Team: Genetics of Breast Cancer

Team Leader: Mrs. Sylvie MAZOYER

- Team staff or staff allocated to the project (according to the dossier submitted to AERES):

	In the report	In the project
N1: Number of professors (see Form 2.1 of the unit's dossier)	0	1
N2: Number of EPST, *Établissement public à caractère scientifique et technologique* (Public scientific and technological institution) or EPIC, *Établissement public à caractère industriel et commercial* (Public industrial and commercial institution) researchers (see Form 2.3 of the unit's dossier)	2	3
N3: Number of other professors and researchers (see Form 2.2 and 2.4 of the unit's dossier)	1	1
N4: Number of engineers, technicians and tenured administrative staff members (see Form 2.5 of the unit's dossier)	1	1
N5: Number of engineers, technicians and non-tenured administrative staff members (see Form 2.6 of the unit's dossier)	2	2
N6: Number of doctoral students (see Form 2.8 of the report unit's dossier and 2.7 of the project unit's dossier)	1	2
N7: Number of persons accredited to supervise research and similar	2	3

- Assessment of work produced and scientific quality:

This research field is highly-competitive. Many results are interesting even if most of them are collaborative (that is the common rule in genetics research). The team has published 38 papers in 5 years, including 15 papers in very good journals with a member of the team as a 1st or last author (Hum Metat (IF=7), Oncogene (IF=7.2), Genes Chrom Cancer (IF=4). Other papers in collaboration, especially with the CIMBA network (Am J Hum Genet (IF>10), Br J Cancer, Hum Mol Genet (IF=7.2)). 9 good international collaborative papers. Most of the major contributions of this team are within national or international consortia

Considering only first author papers: Nice contribution on the non sense-mediated mRNA decay of BRCA genes. One interesting "Human Mutation" paper in 2005 about genomic rearrangements in the BRCA1/BRCA2 genes (well cited), one in "Genes Chromosomes and Cancer" in 2008 about UV in BRCA1 exon 11.

- Assessment of the influence, appeal and integration of the team or the project in its environment:

Overall, these aspects have been judged quite good

6 invitations to scientific meetings.

2 post-docs and 4 Ph.D. students have been recruited.

Major attractiveness of the team is linked to the arrival of Gilles Thomas from NCI in USA (and young people attracted by Gilles Thomas).

External financing is excellent, with 1 international, 1 national and 1 regional grants led by the team. Additionally, the team has got 3 international and 2 national associated grants, as well as many small grants including 3 national (ARC) and 7 regional (League).

The team is well integrated in the international consortia in the field and it has produced multiple papers in collaboration during the last 5 years, including 9 good international collaborative papers between 2005 and 2009 (former and still alive Breast Cancer Linkage Consortium from the FP3, FP4 and FP5 of the European Union). Cooperation within the French national group "génétique et cancer" has also given rise to other nice papers.

- Assessment of the strategy, governance and life of the team or project:

This group is efficient and is well organized.

The 3 projects developed by the 3 PI are complementary to each others. Some internal collaborations within the CRCL. Collaboration with team E9 was quoted by team E9 but not by this team.

Some projects are risky (mitochondrial project for instance) but quite innovative. One team member was recently hired at Centre Léon Bérard and is in charge of the Department.

- Project assessment:

The team might need additional PI or manpower to develop the three projects presented. Some approaches need new high-through put technologies. Others projects are original and risky like the mitochondrial genome project, CNVs, or metabolic approach of BRCA1 actions.

- Conclusion:

  – Overall appreciation

This team has an excellent expertise in developing projects in a highly competitive scientific field.

The mitochondrial genome project, or metabolic (lipids) approach of BRCA1 actions are quite original and might be fruitful. Most of the BRCA1 researchers in the world are involved in the DNA repair or transcription functions. Mitochondrial genome project is based on a new innovative hypothesis and therefore highly risky but quite original. The Dalla-Venezia paper about the interactions between lipid metabolism and BRCA1 function is still the reference on the topic. Some approaches are classical but important and very well performed by the team, others are more original and risky, like the mitochondrial genome project, CNVs, or metabolic approach of BRCA1 actions.

Major expected inputs of the proposed project will probably be with the Thomas's participation to the ICGC (International Cancer Genome Consortium) with the study of breast cancers and the INCa synergie Bio-informatics platform although the specific and original part of the team is poorly described.

  – Strengths and opportunities:

Excellent international and national networks of collaboration have been set up.

Originality of the mitochondrial genome project should be pointed out.

  – Weaknesses and threats:

Outputs are very good but not outstanding considering the FTE of the team

  – Recommendations:

Re-enforce collaborations in the breast cancer field and within the Cancer Research Centre.

Involvement of the head of department in the management of the department should provide added value to this team and others.

E9 Team: Alternative splicing and tumor progression

Team Leader: M. Didier AUBOEUF

- Staff

	Past	future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 and 2.7 of the application file)	2	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	2
N6: Number of Ph.D. students (Form 2.8 of the application file)	2	2
N7: Number of staff members with a HDR or a similar grade	2	2

- Assessment of work produced and scientific quality:

The research of this team is highly relevant, and results are of high quality.

The team has demonstrated its skilfulness and expertise in developing new powerful technology in the field on cancer research (Affymetrix exon array).

12 original papers of high quality have been published in 5 years : 9 with IF >6 and 2 with IF>10. Very good publication record in outstanding international journals is noted.

The Team belonged previously to the UMR 940 INSERM and it joined very recently Lyon (September 09). The PI describes the strategic research projects that he wants to implement thanks to their arrival at the CRCL, specifically through collaborations with teams E8 and E10.

- Assessment of the influence, appeal and integration of the team or the project in its environment:

The PI received the award of an EURASNET young investigator (see below) and an AVENIR grants.

The team includes 1 post-doc and 1 Ph.D. student from Syria. It has trained other foreign students in the past (Brazil, Italy and Spain)

Ongoing collaboration is established with the Genoscope and within the EURASNET excellence network (FP6 2006-2011) (EURASNET aims to explain the mechanisms of alternative splicing and the interference with other regulatory processes)for the development of bio-informatics platform (they develop themselves the FAST DB http://www.fast-db.com/fastdb2/frame.html).

Most of the scientific collaborations are French (5 are quoted)

The major European collaboration is as member of the EURASNET excellence network (FP6 2006-2011; 30 groups) for the development of bio-informatics platform.

An internationally recognised Alternative Splicing database has been established and a small company was founded as a Spin off to support the academic or private research community. The company (Genosplice) is located in the Genopole (http://www.genosplice.com/)

- Assessment of the strategy, governance and life of the team or project:

The team joined the CRCL in September 09. Most members of the team moved from Paris to Lyon. Their arrival should improve the network of collaborations as well as working conditions.

The team shows excellent ability to adapt its expertise to the existing fields of research developed by Lyon cancer teams.

Few teaching activities are quoted in Paris but successful supervision of PhD students and course organization for university students.

- Project assessment:

Highly relevant and promising research lines apply to the exon array expertise for the screening of transcriptome in the cancer models available in the CRC Lyon, including the changes induced by anti-cancer drugs. In addition, work includes mechanistic studies on the effect of cancer-related transcriptional regulators on splicing decisions.

The team's arrival in Lyon has allowed the team to access appropriate models within the CRCL.

It will have access to the "centre de ressources biologiques".

It will have access to a chemical library to screening for inhibitory peptides has been achieved through a national collaboration.

The approach is quite original and promising. The "coupling between transcription and splicing" looks particularly exciting. The group not only has strong expertise in genome-wide transcript analysis with exon-arrays but also a strong molecular biology background in mechanistic analysis of transcription and splicing. The project further includes the novel aspect of translational regulation by transcript variants. This is a unique combination of know-how that puts the group into a very strong position for the analysis of alternative splicing events and its functional consequences in the cancer-related cellular models available at the Center in Lyon. It is still too early to evaluate the fruitfulness of the partnerships in Lyon but it looks promising.

- Conclusion
  - Overall appreciation

This is a good/excellent group. The excellent project combines cutting edge array technology and high-quality candidate gene analysis to elucidate the connected information flow between transcription, splicing and translation.

  - Strengths and opportunities:

The approaches are original.

New technical expertise will be further increased within an European excellence network.

The team benefits of an established exon array platform and bioinformatics for data mining. It demonstrated expertise in molecular studies of candidate genes to provide mechanistic insights.

Potential synergies of this new team within the CRCL are well described, in particularly the strategic enrichment by proteome analysis and the availability of cancer models.

– Weaknesses and threats:

A major weakness is the lack of scientists with stable positions for the different exciting projects: it deserves full support to stabilize and further develop the research conditions

– Recommendations:

This team deserves full support to stabilize the group staff and further develop the research. The connection with the information flow department should be increased for high-throughput transcriptomal sequencing.

E10 Team: Nuclear domains and pathologies

Team Leader: M. Jean-Jacques DIAZ

- Team staff or staff allocated to the project (according to the dossier submitted to AERES):

	In the report	In the project
N1: Number of professors (see Form 2.1 of the unit's dossier)	0	2
N2: Number of EPST, *Établissement public à caractère scientifique et technologique* (Public scientific and technological institution) or EPIC, *Établissement public à caractère industriel et commercial* (Public industrial and commercial institution) researchers (see Form 2.3 of the unit's dossier)	1	3
N3: Number of other professors and researchers (see Form 2.2 and 2.4 of the unit's dossier)	0	0
N4: Number of engineers, technicians and tenured administrative staff members (see Form 2.5 of the unit's dossier)	1	2
N5: Number of engineers, technicians and non-tenured administrative staff members (see Form 2.6 of the unit's dossier)	1	0
N6: Number of doctoral students (see Form 2.8 of the report unit's dossier and 2.7 of the project unit's dossier)	3	2
N7: Number of persons accredited to supervise research and similar	1	3

(5 FTE research scientists + 1,8 FTE technician (permanent) + 2 post-docs + 4 PhD students)

- Assessment of work produced and scientific quality:

The research of this team is quite relevant to cancer with a recent interesting result on molecular alteration in ribosome biogenesis and translational fidelity in a cellular model of human breast cancer progression.

The approach is original, and opens a new field in cancer research.

The team has produced 62 publications in 5 years (about same production between the 5 senior scientists), including 7 papers in IF>10 journals, and 10 in IF>8 journals. 21 papers out 62 (one third) are signed as first or last author by one member of the team. Considering the recent gathering of 5 senior scientists with no common

publication, medium scientific production is quantitatively low (less than 1 paper/year/person in average) and qualitatively medium or medium-low (except when external collaborations are considered). The Team leader has 13 papers in the last 5 years, 5 as last author (3 in low-level journals), 1 as first author in a journal with low IF.

Moreover, the team has deposited 3 patents and others are in progress.

The team was previously in the UMR 5534 CGMC, and this new team now gathers 5 additional senior scientists who develop 5 distinct and partly connected projects.

- Assessment of the influence, appeal and integration of the team or the project in its environment:

No distinctions and no invitations to international events are indicated in the report. 3 communications in 2005, related to the work on herpes virus.

Excellent ability to recruit new staff since the team leader was able to aggregate in this new team new multidisciplinary senior researchers.

Two post-doctoral students are indicated but no information regarding of previous capacity to recruit Ph.D. students and post-docs.

The program relies mainly one grant: INCa "RIBOCAN" coordinated by the team leader. The ARC grant is only partly linked to the team's project (coordinator team E9). Other new grants were obtained and shown in the oral presentation.

Most collaborations are French, no international collaborations except their Switzerland but for only one member of the team.

In the absence of common papers between the senior scientists of the team, cohesive research between team members cannot be evaluated so far and will have to be demonstrated.

- Assessment of the strategy, governance and life of the team or project:

The overall organization looks appropriate for the presented scientific objectives. Governance is clearly presented. There is an appropriate correlation between the projects and the human resources. Nevertheless, different PIs are aggregating in the team and will have to interact and work in a coordinated manner in order to develop the team. The challenge for this team will be the organization and management of the PIs aggregation, in the next few years.

Major efforts were made to build this new team with 5 senior scientists from different fields, with a clear chart of the overall organization of human resources and of the coordinated projects

Teaching activities are mainly linked to one member of the team.

- Project assessment:

The project looks feasible considering the 3-years preparation of their move from virus to cancer research, and the first interesting results obtained in breast cancers.

The French RIBOCAN network granted by INCa should further support the long-term development of the project.

The team has access to the "biological resource centre"

The scientific project is original and might be at risk. Considering the hypothesis that ribosomes are altered in tumour cells the team will have to prove their role in oncogenesis and cancer chemosensitivity.

The field of the project is probably not yet highly competitive.

- Conclusion

  - Overall appreciation

This is a new team, with new projects on cancer initiated 3 years ago, exploiting the “know how” on the evaluation of the functional role of the nucleolar organization and mainly ribosomal function. Although the team leader has been well trained in ribosome research, his more recent work rather deals with viruses. The decision to focus on cancer was recent within the CRCL but well described and organized.

  - Strengths and opportunities:

Multidisciplinarity.

The research theme is a niche in the cancer research field.

  - Weaknesses and threats:

The team lacks international network and collaborations

The use of the C. Elegans model to recapitulate the human model is risky.

Cohesive research between team members will have to be demonstrated.

  - Recommendations:

The team needs to find one appropriate model.

It should favour the collaborations with the E8 team within the department.

E11 Team: Estrogen signalling and breast cancer

Team leader: Mrs. Laura CORBO

- Team staff or staff allocated to the project (according to the dossier submitted to AERES):

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	2
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)	2	4
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	6
N7: Number of staff members with a HDR or a similar grade	2	3

- Assessment of work produced and scientific quality:

The team studies the role of ER signaling and its regulation in breast cancer development and resistance to treatment. The work is focused on the characterization of the molecular mechanisms regulating estrogen receptor alpha (ERalpha) genomic functions and on the role of ERalpha methylation in estrogen extranuclear signaling. The most important findings include the demonstration of novel post-translational regulations of ERalpha activity : (i) sumoylation of the ERalpha regulates its transcriptional activity. (ii) arginine methylation of ERalpha DNAbinding domain by PRMT1 (Protein Arginine MethylTransferase regulates its extra-nuclear function (Molecular Cell, 2008).

The team published very good papers, e.g. Mol. Cell 2008, J. Cell Sci. 2007, Oncogene 2007. The publication score has diminished recently but should increase with the recent integration of two high level staff scientists, and with the development of new projects.

Overall, there were 46 publications in the last 5 years, including 12 publications signed by at least one member of the team as first or last corresponding author, and 24 corresponding to collaborative work. Of note, 16 of these publications correspond to clinical work, signed by an MD alone. 5 publications correspond to previous post-doctoral work outside of the team. One patent application (Europe and US).

- Assessment of the influence, appeal and integration of the team or the project in its environment:

The work on arginine methylation of ERalpha by PRMT1 (Molecular Cell 2008) has been world-wide recognized with a citation in Faculty of 1000 and several invitations and selected oral communications in international meetings (Croatia, Italy, Spain, Canada, USA), including EMBO conferences and FASEB meeting.

The team includes 15 members, with a good balance between staff scientists, technicians and PhD students. Two Post-docs have been recruited during the last quadrennial, including one foreigner.

External collaborations with French (Montpellier (IRCM), Strasbourg (IGBMC), Paris (Curie), Grenoble) and foreign (University of Montreal, Canada) groups are mentioned.

There are several other French teams working on the same questions. Fortunately an “ARC libre” project links two of those.

- Assessment of the strategy, governance and life of the team or project:

The organization of the team is very good. The team is composed of both researchers and MDs. One of the staff scientists is presently co-head of the Genomic platform of the Canceropole Lyon Auvergne Rhone-Alpes.

The group leader frequently participates to M2 defence committees (12 h/year), committees for doctoral fellowships attribution (36h/year), and to HDR and PhD committees (8). During the last quadrennal, she held positions at the French CNRS Scientific Committee (Comité National) and ARC Scientific Committee (Commission régionale 4 de l'ARC Sud Est).

- Project assessment:

This is a well focused program on the role of ER. The studies will try to define ER regulation (methylation, sumoylation), new partners and mechanisms of resistance to drugs. There are several issues that are not completely convincing and need be improved. The use of cell lines may introduce bias, the study of tumor samples is too limited and should be developed. A mouse knock-in model is being generated to address the physiological relevance of ERalpha methylation by PRMT1. This part of the project is ambitious and risk-taking.

Existence and relevance of a resource allocation policy: not easy to assess from the provided documents. However, the team is “équipe labellisée LNCC” and is also associated to an “ARC libre”.

- Conclusion:

  – Opinion:

This team is very good with promising results that need to be further developed. Some aspects of the project would request additional arguments.

  – Strengths and opportunities:

The regulation of ERalpha by PRMT1- mediated arginine methylation is an interesting basis for future projects. The presence of an MD in the team provides clinical connections opportunities. A collaboration was set up to generate the knock-in mice.

  – Weaknesses and threats:

The leadership of the various projects is not clear. The connection between the different subgroups (basic versus applied projects) has to be improved.

  – Recommendations:

The team should focus on the most solid previous observations.

E12 Team: Signalling, Metabolism and Tumor Progression

Team leaders: Mrs. Ruth Rimokh and M. Germain GILLET

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

	Past GG	Past RR	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4	0	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2, 2.4 and 2.7 of the application file)	0	1	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	0	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	1	1
N6: Number of Ph.D. students (Form 2.8 of the application file)	5	0	4
N7: Number of staff members with a HDR or a similar grade	2	1	2

- Appreciation on the results

The team associates two previous labs. One lab has moved its focus from B-cell CLL towards TGF-ß signalling following their important work that identified the FLRG modifier in a translocation. The characterisation of FLRG expression and properties was original. The subsequently developed analysis of TGF-ßR signalling events (interplay Smad4 and TIF1γ; sumoylation) are relevant although this topic is highly competitive.

The other lab studied the role of oncogenic src in the deregulation of apoptosis and identified a link between proteasome activity and degradation of the Bcl-2 family member Nrh. Synthetic peptides that can interfere with Bcl-2 proteins were studied and found to trigger apoptosis. Unexpectedly, the characterisation of Nrh led to the identification of a role in cytoskeleton organisation during embryo development, and possibly in EMT.

In general, the results reveal promising aspects to be explored but lacked a major impact on the field. In comparison to many other groups in the project, this team appears to provide some promising future research plans, however, it is recommended that the team makes a serious effort to reach higher international impact and visibility by means of stronger publication and possibly more focused research efforts.

The number of publications is good with an average of 2 papers per year in good journals (IF 4-8) but should increase considering the size of the new team. it is also commendable that this team shows a large number of collaborative publications with many of the other teams in the project. A good record of PhD theses is noted.

The E12 team has recently been created by the merge of two pre-existing groups. The rationale of this merge is not clearly explained, though a clear result is that the team now gathers a tremendous expertise that spans many areas of research. As a result, a large number of specific projects are proposed.

Mostly local or national collaborators are mentioned.

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

2 invitations to conferences over the past 5 years are indicated. No specific awards are listed. The team counts a good number of national Post-docs and PhD students. Both groups have shown constant ongoing fund raising efforts. Mostly low budget grants (25 000€ or less) have been obtained, but few international grants. Few or none networks or foreign partnerships are mentioned. Three patent have been deposited, including one patent on therapeutic us of peptide aptamers.

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

Scientific activities should be more focused.

The team makes serious efforts to introduce new research focus and initiatives. The best example is the proposed work on mitochondrial metabolism and its relevance to TGF-ß signaling, the process of EMT and breast cancer progression. This is a new research avenue for the team and promises novel findings. The team also actively works with the TGF-ß pathway and the role of TIF1γ. This research presents both positive and negative points as it partially overlaps with the research of others teams (e.g. E6, E15). This overlap has positive attributes that promise future collaborations between the teams of the project as it has already happened. However, the strong focus on TIF1γ might generate some aspects of internal competition, which may not be very productive as this field is highly competitive at the international level. For example, E12 performs genome-wide transcriptomic analysis in breast cells after TIF1γ knockdown, whereas E6 performs genome-wide transcriptomic analysis in pancreatic cancer after tissue-specific knockout of TIF1γ. Although the two tissue types are distinct, it is anticipated that these experiments will reveal many common gene targets. Collaboration on these projects would be advisable, however, the committee could not clearly see such immediate plans. Thus, caution and better research coordination with the other 2 teams is warranted for the best possible success of this project.

2 members of the team are University teachers. One of them is a member of an INSERM scientific committee (CSS7).

- Appreciation on the project

This team results from the fusion of two previous research groups who found a common line of interest centered around the effects of TGF-ß on breast cancer cells. They will continue to study previously established signalling mechanisms downstream of the TGF-b receptor (Smad/TIF1γ /sumoylation interplay), especially those linked to EMT. They will also bring in know-how to strengthen the EMT studies, in particular by analysing the effect of TGF on mitochondrial and glycolytic metabolisms, as well as the role they found for Bcl-2 family member Nrh in cytoskeletal dynamics. The previous data on which the common project is based are sound and the research plan thus feasible.

The role of metabolic tumour cell adaptation in the EMT process downstream of TGF-b is very original and a poorly explored concept. The results may lead to a deeper understanding of the mechanisms leading to the escape of tumour cells from the primary tumour to form metastasis. However, with the analysis of TGF-bR signalling events (interplay Smad4 and TIF1g; sumoylation) the group enters into a highly competitive and risky area.

- Conclusion

  - Overall appreciation

This team results from the fusion of two previous research groups that found a common interest around the effects of TGF-b on breast cancer cells. This is an important area of research, especially regarding EMT, but the project would have deserved being more focused.

– Strengths and opportunities

A major strength relies on the effort of reorientation of both groups towards a common research priority. The team size should allow to achieve a good critical mass. The two group leaders seem to appreciate each other since a long time and to be eager to join their efforts in the future.

– Weaknesses and threats

The expertise for the proposed studies on glucose and mitochondrial metabolism is recent in the team with little scientifically documented productivity. The studies of TGF-bR signalling events (interplay Smad4 and TIF1g; sumoylation) enter a highly competitive field.

– Recommendations

The research program needs to identify priorities and to be focused.

The expertise on metabolic tumour cell adaptation should be strengthened.

The studies on TGF-bR signalling events are risky so that the data, especially the proposed screen for EMT inhibitors, should seek to identify original results to pursue and build on in the future.

E13 Team: Therapeutic targeting of the tumor cells and of their immune environment

Team leaders: M. Christophe CAUX and M. Jean-Yves BLAY

- 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	2
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	7
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	5
N6: Number of Ph.D. students (Form 2.7 of the application file)	9	8
N7: Number of staff members with a HDR or a similar grade	7	6

- Appreciation on the results

The scientific projects performed by this team these four past years is of very good overall quality. Both leaders contributed to the identification of new and original mechanisms of immune evasion. The main contributions are the observations that plasmacytoid dendritic cells are functionally altered in the tumor microenvironment and that Treg are associated to tumoral progression. Some targets involved in the inhibition of pDCs and in the mechanism of action of Treg have been characterized. Another important aspect of the research developed by this team concerns the impact of various cell death pathways on antitumor immunity. The third point tackles more clinical questions and among them combined therapeutic strategies associating a cytotoxic drug with an immunotherapy based on the activation of DC.

Globally this team published a plethora of articles (110) during these five past years. Among them 30 are princeps papers from the group (Cancer Res X 4, J Clin Oncol X 2, Eur J Cancer X 7, JBC, J Immunol, Oncologist X 2, Int J Cancer....). The national and international collaborations have allowed also publication in high impact factors journals including J Exp Med, Immunity, Blood, PNAS. Both team leaders have a strong national and international recognition in their fields of competence. This is attested by numerous invitations in national and international meetings.

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

The two team leaders are regularly invited to conferences . The group recently hired one young researcher. Excellent ability is indicated by the success in obtaining grants from INCA, Ligue, CLARA and industry. Among others one can indicate a group working on dendritic cells in Grenoble, two excellent teams in Dallas and in Houston, TX. Multiple partnerships with Pharmas: Innate Phamram, ImmunoID, Novartis, GSK

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

Original and efficient association of a clinician with a long standing involvement in clinical research and a full time researcher. The PIs have recently embarked projects going from bedside to animal models that should provide important insights in breast cancer studies (for instance PDC and breast cancer). Team members are involved in Master teaching and part of the CLARA as scientific director and Axis II coordinator, head of the FACS and TLR platforms.

- Appreciation on the project

The proposal is in line with the previous one. The two main objectives of the project aim at deciphering mechanisms of immune subversion by cancer cells to validate therapeutic strategies targeting both tumors and their immune environment using pre-clinical models and to translate these concepts in patients. The project is very attractive and innovative and addresses a great number of interesting questions including the role of pDC and Treg in breast, ovarian carcinoma and sarcoma. The team develops also innovative approaches to functionally characterize immunosurveillance and escape mechanisms, validates also combined therapeutic strategies targeting oncogenes and the immune system in rodent models and finally develops clinical trials in patients. The research program is therefore a pertinent mix of basic and clinical research.

The PIs have proved highly efficient in obtaining funds (INCA, RTRS, industry).

Important new projects are being developed in animal models to study clinical observations. The study of TAA following chemotherapy is new and challenging.

- Conclusion
  - Overall appreciation

This project explores a plethora of questions concerning tumor immunosurveillance, escape mechanisms and therapeutic strategies targeting both oncogenes and the immune system. The program is highly ambitious and even though all the aspects are pertinent and interesting, focusing on the more competitive aspects could improve further the project.

  - Strengths and opportunities

The proposed program is an excellent mix of basic and clinical research. Both co-leaders have a strong national and international recognition in their respective domains. They both showed great competence in obtaining fundings and participated also in European networks of excellence. The activity of valorisation is also of great quality with numerous patents. The team has established an excellent network of local, national and international collaborations.

– Weaknesses and threats

The program is very vast with probably a too large number of questions.

– Recommendations

To improve competitiveness the team leaders could focus on the more internationally relevant aspects.

E14 Team: Innate Immunity Signalling and Oncogenesis

Team leader: M. Toufic RENNO

- Staff members

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

Team 14 « Innate Immunity Signaling and Oncogenesis » was formerly attached to the UMR5201 CNRS.

- Appreciation on the results

The science developed by this team these past four years is of overall good quality. The team made two original and important contributions in the field. First, it has shown that MyD88 is an important mediator of Ras signaling and transformation. Second, it identified TLR3 as a death receptor. Both observations were original and competitive in the field.

The team has published 27 papers these past four years. The overall recent publication score is good with two princeps publications in 2006 and 2007 in good specialized journals : The Journal of Immunology and Gastroenterology. A collaborative paper was published in Mol Cell Biol in 2005. The team has also filed seven patents.

- 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 established in the frame of this project several national and international collaborations and set-up several interactions and contracts with pharmaceutical industries (Genentech and Erytech Pharma). So far, the lab members are essentially post-docs and PhD students with no permanent scientist except the team leader. As mentioned above the team leader has shown great competence to obtain competitive grants. For instance the team leader is the coordinator of an ANR Blanc contract and the PU/PH of an Inca grant.

The team leader showed also impressive competence in obtaining grants (ANR, ARC, LNCC, PDC CLARA) and contracts with the industry (Average of 400 kEuros each year).

The attractiveness of the team is attested by the recruitment of 3 Post Docs and 3 PhD students. This should allow a good development of the proposed project.

Very efficient fund raising through ANR, INCa, Industry

One collaboration is indicated with Genentech

Collaboration with Erytech Pharma

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

The team was only recently created after the previous Unit closed. The team leader is dynamic and has structured a small group with some PhDs. The team is highly efficient although the number of full time researcher is low. The project is highly focused on cutting edge project on the role of Myd88 and TLR3 signaling in cancer apoptosis which is a very good point. The activity is restricted to one permanent scientist and one PUPH.

Highly focused on cutting edge project on the role of TLR3 and MyD88 signaling in cancer apoptosis

Teaching activity is restricted to one PU-PH.

- Appreciation on the project

The project, in direct line with the previous activities is innovative and has two main objectives. The first one is to decipher the role of MyD88 in cell transformation. This aspect includes the study of the relevance of the Erk-MyD88 interaction in vivo. The second aspect will analyze the role of the TLR3/TRIF axis in the apoptosis of cancer cells. This second part is based on the observation that activation of TLR3 can trigger apoptosis of different types of human cancer cells. The molecular basis of the sensitivity to TLR3-mediated apoptosis (pro-apoptotic vs pro-inflammatory complexes) and the nature of the recruited molecules will be more specifically analyzed. Another very original point concerns the study of the role of TLR3 cleavage in regulating sensitivity to apoptosis and/or inflammation. All aspects are quite original and interesting and may have important clinical implications including the opportunity to set-up clinical trials. The technological strategy including animal models looks pertinent and well adapted. An excellent ability to obtain grant has been also noted.

The project is original and should provide opportunity to set-up clinical trials.

- Conclusion

  - Overall appreciation

In conclusion, this team develops an innovative and competitive research program in the field of cancer biology. Both aspects are original and have a good overall feasibility. The record of publications these past four years although good will be certainly improved in the future.

  - Strengths and opportunities

This is an original, innovative and well-focused project headed by a dynamic leader with a good record of publications considering that the team moved recently. Ongoing research is very promising and should help to improve further the quality of publications. The leader has showed outstanding ability in obtaining important fundings. The activity of valorisation is also excellent with not less than 7 patents. The integration of the team in the CLB is also a very good point. There are also many interesting potential clinical applications.

  - Weaknesses and threats

The only identified weakness is related to the limited size of the team with only one full time researcher.

– Recommendations

To succeed, this team will have to recruit a full-time researcher in order to improve the critical mass and visibility of the team. Also, an important point is to continue to develop collaborations with other teams at the CLB.

E15 Team: TGF-beta and Immune Evasion

Team Leader: M. Julien MARIE

- 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)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
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)	1	1
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

This team is investigating the role of TGF-beta in immune evasion. The researchers of this team have recently generated mice with T cells that do not respond to TGF-beta (cell-specific deletion of TGF-ß receptor) and mice with constant TGF-beta signaling in their T cells (T cell-specific expression of an activated form of TGF-ß receptor). These models allowed them to address the role of TGF-beta signaling in T cells. In this respect, they have demonstrated that mice deprived of TGF-beta signaling in their T cells develop rapid extremely severe autoimmune symptoms. In addition the team has demonstrated that TGF-beta is required for Foxp3+ regulatory T cell and CD1d-dependent NKT cell development.

The team has described that TGF-beta controls the development of highly cytotoxic T cells expressing hallmarks of NK cells.

During the last years, the team has published 10 publications (IP>20: 1, IP>15: 3, IP>6:7) in very good journals, including 5 original papers with the PI as last author in J Exp Med, Immunity and Genesis.

The team has filed an international patent.

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

The attractiveness of this very young team could be improved. It has a very good visibility locally and at the national level.

This young team has recruited PhD students and post-docs including from the USA.

The PI has obtained awards from the SFI, the city of Lyon, and the Academy of Sciences of Lyon.

The team was successful in obtaining several grants from charities, and national agencies. The team has established several international collaborations (University of California, San Francisco, NCI, NIH Bethesda and IGBMC, Illkirch) as well as collaborative projects within the CRLC (Teams E6 and E12). Multiple grants were obtained including the prestigious ERC grant.

Stable and fruitful collaborations are noted.

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

This small team has started a very efficient program investigating animal models dedicated to TGF b signaling together with collaborators from the CRLC. The team, though small, is very productive and well connected with the other “TGF” groups as well as its department.

- Appreciation on the project

The objective of the team is to discriminate which cells of the immune system could be the main target cells of TGF-ß regulatory effects. Although the projects look feasible, it would be important to increase the researcher potential able to address the number of questions raised by the team.

The project is highly competitive at the international level.

- Conclusion

  – Overall appreciation

This team is conducting a very original project in the field of tumor immunology. Understanding the role of TGF-beta in shaping the stroma and the immune system is of fundamental interest in the field of cancer biology and immunotherapy.

  – Strengths and opportunities

This initiated collaborative project is indeed a good opportunity for this young team. The team had developed essential tools to decipher the role of TGF-beta signaling in T cells. The proposal is very ambitious and links immunology and oncology and opens new perspectives for future clinical approaches.

Clearly, the team has clear lead-over in the field. The pertinence of the topic will facilitate to attract motivated postdoctoral fellows and PhD students.

  – Weaknesses and threats

Major weakness is related to the extremely limited size of the team and lack of full time senior researchers.

– Recommendations

Focus on competitive aspects of the project (ie ncNKT);

Restrict the project to a limited number of animal models;

Recruit additional team members.

E16 Team: Mechanisms of chemoresistance to cytotoxic nucleoside analogues tubulin binding agents and therapeutic monoclonal antibodies

Team leader: M. Charles DUMONTET

- 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)	8	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	5	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	6	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	13	0
N7: Number of staff members with a HDR or a similar grade	10	3

- Appreciation on the results

The common theme of this team is devoted to the study of novel therapeutic approaches in the field of cancer. Six groups have been developing the following subprojects: resistance to nucleoside analogues, tubulin binding agents and monoclonal antibodies; epigenetic alterations in cancer; stem cells in hematological and breast cancers ; hormonal therapy of breast cancer ; ABC proteins in breast cancer ; chemoresistance mechanisms in acute leukemias.

The team has focused on the characterization of new active compounds and identified and patented antimitotic chalcones displaying strong activity in vitro and in human xenotransplants.

The team is clearly developing robust and reproducible in vitro and in vivo models to better understand the mechanisms underlying a primary or secondary failure of these immunologic treatments in patients. The aim of this team is to investigate the mechanisms of action of anticancer monoclonal antibodies and the mechanisms of resistance to these biomolecules.

The team is composed of physician/researchers, a post-doc, PhDs and technicians possesses expertise in preclinical (in vitro and in vivo) modeling as well as in translational research, including the identification and validation of prognostic/predictive factors in clinical samples and the development of novel agents or therapeutic strategies.

The originality of the team research is high and the project is very innovative.

The team has published 176 papers since 2005, about one half in basic and one half in clinical research, mostly hematology. Among original publications, 71 have a member of the team as first or last author, including occasionally some papers in excellent journals such Blood and Clin Cancer Res. About 20 articles of review have been published in national or international journals, usually with low IF. 7 theses were defended in the last four years, 4 patents were filed.

The team is involved in several important international collaborations and outstanding participation in national networks. However, with regard to the scientific excellence of the team, invitations to international meetings have to be improved, and team's ability to recruit post-docs and researchers is limited.

Success in getting funding from several agencies is excellent. The team is constantly supported by INCA and has good interaction with pharmaceutical industries resulting in numerous grants.

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

The project on therapeutic monoclonal antibodies is highly relevant for the CRLC although highly competitive. The team members have multiple administrative charges at the University the Lyon Biopole and CLARA.

- Appreciation on the project

The general aim of the team is to investigate the resistance mechanisms to anticancer agents, to identify and validate factors associated with response to therapy, and to develop strategies to restore cancer cell sensitivity: principally an interesting project. The specific aims of the team project are devoted to identify the nature and role of accessory cells involved in the anticancer activity of Mabs, identify novel apoptotic signalization pathways induced by these antibodies, develop novel sensitization strategies and determine the clinical relevance of the observations made in preclinical models.The approaches appeared clear. This is the "backbone" of this team's project and as such it appears very encouraging for the future of the team. Overall the project has a number of very innovative and interesting aspects. Innovative aspects and good feasibility are worth mentioning.

- Conclusion

  – Overall appreciation

The team presents a very innovative project with good feasibility and scientific potential. The group has lifted an original project. It is well funded, has an interesting research portfolio and is gaining international recognition. The project would benefit from attracting full-time senior researchers

  – Strengths and opportunities

The project shows a high degree of originality in a cell type that is technically challenging. The strength is the strong reasearch experience of the team leader in the field of anti cancer therapies including chemotherapies and therapeutic mAbs. Also the current funding seems to be solid. The strong implication of oncologists and hematologists in research project, the close ties with hospital wards, multicentric research groups and pathologists, the expertise in preclinical modelling and translational research, the rich network of academic collaborators and pharmaceutical companies, the expertise provided by other researchers in the Immunology, Inflammation and Virology departments are important opportunities and added value to this group.

  – Weaknesses and threats

  – Recommendations

Focus;

E17 Team: Mechanisms of chronic hepatitis B and C pathogenesis and novel antiviral strategies

Team leaders: M. Fabien ZOULIM and Mrs. Lucyna COVA

- 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)	4	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	5	5
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)	5	4
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	4	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	8	6
N7: Number of staff members with a HDR or a similar grade	10	10

- Appreciation on the results

The E17 team was previously part of the Inserm unit U871. The excellent quality and impact of its research for virus-induced hepatocellular carcinoma places this team among the leading teams of the center and at the top of the department.

Research is focussed on two major axes: one on HBV and one on HCV. For HBV there are three topics: (i) Hepatitis B virus (HBV) persistence and pathogenesis, (2) innate responses and (3) HBV immunotherapy. For HCV, there are also 3 topics: (1) HCV and glucose metabolism, (2) lipid metabolism and HCV assembly and (3) the identification of proteins associated with viral particles. Productivity and impact is excellent as indicated by the quality and number of publications and its citations, number and quality of presentations, invited conferences, patents and external funding.

The team is internationally recognized for its cutting-edge work on mechanisms of HBV pathogenesis, HBV immunotherapy and diagnosis and management of HBV resistance. A major strength of the team is its translational research. Within this field the team is clearly among the leading teams world-wide. Within the last years, the team has successfully enlarged its scope by extending its work on the study of hepatitis C virus (HCV)-host interactions. This emerging axis is further strengthened by the recent recruitment of excellent young talents who are forming a new group within the team focusing on lipid and glucose metabolism and the HCV life cycle.

The research addresses key questions in the field, uses state-of-the-art methodology, is highly innovative and original and has a major impact for the understanding of the pathogenesis of viral hepatitis and diagnosis and management of HBV resistance. Furthermore, several innovative novel antiviral strategies have been developed resulting in six patent applications.

The number, quality and impact of publications is excellent, both for papers originating directly from the lab's work and for those resulting from collaborations. The team regularly publishes in the top journals of the field including Hepatology, Journal of Hepatology, Journal of Virology, Gastroenterology and AIDS. Furthermore, the team has published many highly cited state-of-the-art reviews in top level general journals and the team leader is regularly contributing to the international guidelines for the treatment of hepatitis B.

The team has presented a large number of oral and poster communications at all major international conferences of the field (International HCV and HBV Meetings, AASLD, EASL, ISVHLD).

Furthermore, the team has filed 6 highly original patents demonstrating the ability not only to be highly productive but to valorize their results.

The team leader is regularly invited to give state-of-the-art lectures and serves as a chairman at the leading international scientific meetings in viral hepatitis and hepatology. He has been or is serving on the editorial boards of the leading scientific journals in the field as well as in the governing boards of the major scientific organisations in Hepatology (EASL, AFEF). Furthermore, he is regularly himself organizing international meetings on viral hepatitis of the highest standard and has shown to attract the most brilliant speakers in the field. Finally, he has been the coordinator of a large EU network of excellence focussing on viral resistance.

Thus, this excellent publication, patent, presentation and conference record clearly documents the outstanding productivity of the team and the international leadership role of the team leader in the field of viral hepatitis and antiviral resistance.

The partnerships are of the highest quality and include the top-level partners in the field.

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

The impact of the research performed is excellent and of high impact for the field as shown by the originality of the projects, the excellent quality of the publications and the ability to attract top level funding. Attractiveness of the unit is high because the project is well focused, innovative and is based of knowledge and tools which have been developed in the lab (such as assays to investigate HBV resistance). Another highly attractive point is the strength in translational research with initiation and participation of clinical trials incorporating concepts or tools developed in the unit. The unit is well connected on a local, national and international level. These include interactions with the Lyon University Hospitals, the Cancer Center, the ENS, but national also national networks funded by the ANRS and INCA and international collaborations with other leading teams in the field.

The number and reputation of awards is high. The team leader has received the prestigious academic Palm of the University of Lyon in 2008 – this French award is given for major contributions to French national education. The team has presented a large number of oral and poster communications at all major international conferences of the field (International HCV and HBV Meetings, AASLD, EASL, ISVHLD). Furthermore, the team has filed 6 highly original patents demonstrating the ability not only to be highly productive but to valorize their results. 6 PhD students finished their thesis. The team leader is regularly invited to give state-of-the-art lectures and serves as a chairman at the leading international scientific meetings in viral hepatitis and hepatology. He has been or is serving on the editorial boards of the leading scientific journals (Hepatology, Antiviral Research) in the field as well as in the governing boards of the major scientific organisations in Hepatology (EASL, AFEF). He serves as associate editor for J. Hepatology and J. Antimicrobial Chemotherapy. Furthermore, he is regularly himself organizing international meetings on viral hepatitis of the highest standard and has shown to attract the most brilliant speakers in the field. Finally, he has been the coordinator of a large EU network of excellence focussing on viral resistance (VIRGIL).

During the last years the team leader has demonstrated his ability to attract excellent young talent in the field by recruiting a very experienced scientist from Inserm - ENS Lyon (CR1) and a young scientist returning from an excellent US lab at the Fred Hutchinson Cancer Center in Seattle (CR2). Another postdoc from the US has recently joined the unit. This remarkable recruitment of several talented young scientists with an excellent scientific track record illustrates the attractiveness of the unit and its leader and allows the development of the novel and highly competitive project focussing on the pathogenesis of HCV infection. This recruitment of young talent within the last years is clearly a major strength of the team and will be an asset for its future quality and productivity.

The ability to raise funds, to successfully apply for competitive funding, and to participate to scientific and industrial clusters is excellent. This is illustrated by the large number and high volume of external funding including INCa, ANRS, EU. The team leader has been the coordinator of the EU network of excellence VIRGIL, illustrating his leadership role and his ability to obtain EU funding as a head of a large multinational cluster and network of excellence. Furthermore, the team is supported by substantial grants by the pharmaceutical industry further

underlining the impact of their research for patient care. The unit obtained more than 400 kEuros par year in external funding. The team is part of many scientific and industrial clusters.

The team participates at all major scientific networks of the field. These include (among others) the European VIRGIL Network of Excellence (drug resistance and development of new drugs), the national ANRS and Canceropôle Networks. The team is involved in numerous clinical trials and clinical investigations including highly innovative trials on novel approaches for antiviral treatment.

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

The scientific strategy is excellent and addressed key questions in the field. The team leaders have excellently focused the projects on two major axes that are interconnected. The team leaders have a long-standing excellent track record in governance.

The unit is well organized as shown by the efficient structure to monitor progress and solve technical and administrative problems. Internal and external communication is excellent. A structured and detailed weekly organisation of the unit was presented.

The coordination by the team leaders is excellent and internal collaborations allow synergies which are in particular important for initiation of novel projects in the field of HCV-host interactions. The team has several cutting edge projects such as the HBV immunotherapy and innate immunity axes. Risk taking is an important part of their strategy as illustrated by several highly innovative projects. In the field of HCV the team has embarked on the challenge of developing novel model systems to better study HCV-host interactions.

The team leader is Professor of Medicine at the University of Lyon and Director of the Liver Unit at the Lyon Hospitals and has a very active responsibility in teaching undergraduate and graduate medical and PhD students as well as interns and residents at the hospital. Furthermore, he actively directs or organizes regularly postgraduate courses for hepatologists and gastroenterologists both at the national (AFEF) and international level (EASL). Most recently he has taken the responsibility for postgraduate education in hepatology at the EASL Govering Board. This appointment clearly shows his commitment and for teaching activities and his international reputation in postgraduate education of physicians and scientists. A team member is a lecturer for animal experimentation course. All other principal investigators actively participate in the education of undergraduate students (M1, M2) and PhDs.

The team leader plays a major role in the organisation of local research at Lyon as illustrated by his position as a coordinator of the Infection and Cancer coordinated action in the Rhône-Alpes Cancéropole.

- Appreciation on the project

Research is focused on two major axes: one on HBV and one on HCV. For HBV there are three topics: (i) Hepatitis B virus (HBV) persistence and pathogenesis, (2) innate response and (3) HBV immunotherapy. For HCV, there are also 3 topics: (1) HCV and glucose metabolism, (2) Lipid metabolism and HCV assembly and (3) identifications of proteins associated with viral particles. The team is internationally recognized for its cutting-edge work on mechanisms of HBV pathogenesis and persistence and HBV immunotherapy. A major strength of the team is its translational research. Within this field the team is clearly among the leading teams world-wide. Within the last years, the team has successfully enlarged its scope by extending its work on the study of hepatitis C virus (HCV)-host interactions. This emerging axis is further strengthened by the recent recruitment of excellent young talents who are forming a new group within the team focusing on lipid and glucose metabolism and the HCV life cycle.

The research addresses key questions in the field, uses state-of-the-art methodology (cutting-edge virus model systems, appropriate animal models for preclinical evaluation of immunotherapies), is highly innovative and original and has a major impact for the understanding of the pathogenesis of viral hepatitis and the development of urgently needed novel antiviral strategies. All the methodology, knowledge and infrastructure to execute the project is established at the lab, the goals are realistic and the project is feasible.

The resource allocation policy of the team regarding external grant applications has been clearly described and comprises contribution to the common budget as well as part of the budget being specifically allocated to the principal investigator who wrote the grant.

The program is highly original and is well balanced between low and high risk projects.

- Conclusion

  - Overall appreciation

The E17 team, originating of Inserm U871, comprises 6 tenured scientists, one postdoc, several medical doctors, 3+3 ITAs and 8 PhD students. The excellent quality and impact of its research for virus-induced liver cancer places this team among the leading teams of the center and at the top of the department. Research is focused on two major axes: one on hepatitis B virus (HBV) and one on hepatitis C virus (HCV) infection. Viral hepatitis is a major cause of hepatocellular carcinoma and thus of major relevance and impact for the cancer center. For HBV there are three topics: (i) Hepatitis B virus (HBV) persistence and pathogenesis, (2) innate response and (3) HBV immunotherapy. For HCV, there are also 3 topics: (1) HCV and glucose metabolism, (2) Lipid metabolism and HCV assembly and (3) identification of proteins associated with viral particles. Productivity and impact is excellent as indicated by the quality and number of publications and its citations, number and quality of presentations, invited conferences, patents and external funding.

The team is internationally recognized for its cutting-edge work on mechanisms of HBV pathogenesis and persistence and HBV immunotherapy. A major strength of the team is its translational research. Within this field the team is clearly among the leading teams world-wide. Within the last years, the team has successfully enlarged its scope by extending its work on the study of hepatitis C virus (HCV)-host interactions. This emerging axis is further strengthened by the recent recruitment of excellent young talents who are forming a new group within the team focussing on liver metabolism and the HCV life cycle.

The research addresses key questions in the field, uses state-of-the-art methodology, is highly innovative and original and has a major impact for the understanding of the pathogenesis of viral hepatitis and the development of urgently needed novel antiviral strategies. All the methodology, knowledge and infrastructure to execute the project is established at the lab, the goals are realistic and the project is feasible. The program is well balanced between low and high risk projects.

The team should continue the original and excellent program and strive for their ambitious goals. This team will certainly play a major role in its field within the next years and should receive support with high priority.

  - Strengths and opportunities

The strength of the team is the originality and impact of the project including a major focus on translational research, the exceptional recruitment of young talent including scientists from abroad, the outstanding productivity, its leadership role in the field of viral hepatitis, its ability to attract large volume of external funding and its high international visibility. This team will certainly play a major role in its field within the next years.

E18 Team: Hepatocarcinogenesis and viral infection

Team leaders: M. Philippe MERLE and Mrs. Isabelle CHEMIN

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	9	7
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)	9	6
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	3
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	2	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	6	5
N7: Number of staff members with a HDR or a similar grade	12	9

- Appreciation on the results

The E18 team, originating of Inserm U871 is co-directed by two PIs, one researcher with clinical activities and the other is a basic researcher.

The very good and important impact of its research for hepatocarcinogenesis places this team well into the cancer center. Hepatocellular carcinoma is a leading cause of cancer death world-wide and therapeutic options are very limited. Research is centered around three axes including (1) early steps of neoplasmic transformation of liver cells and interplays with viral infection, (2) HBV-induced hepatocarcinogenesis and a very original, important and strong translational axis comprising (3) clinical trials. Productivity and impact is very good as indicated by the quality and number of publications and its citations, number and quality of presentations, invited conferences and external funding.

The team is internationally recognized for its translational research in viral hepatitis, occult HBV infection and mechanisms of hepatocarcinogenesis. A major strength of the team is its translational research with original clinical trials where the team has an excellent track record and experience as indicated by the number and quality of trials and the leadership role played in these trials (as a PI or coordinator).

The research addresses key questions in the field, is innovative and original and has a major impact for the understanding of the pathogenesis of and treatment of hepatocellular carcinoma and viral hepatitis.

The number of publications is very high (>200). The impact and quality of the publications is excellent. The team regularly publishes among the best journals of the field including Hepatology, Journal of Hepatology and AIDS. Furthermore, the team has published many highly cited state-of-the-art reviews in top level journals. It is worth noticing that publications are frequently shared with team E17 as both teams are presently included in the same Inserm Unit.

The team has presented a large number of oral and poster communications at all major international conferences of the field (AASLD, EASL, ISVHLD).

Two team members have co-filed 6 highly original patents demonstrating the ability not only to be highly productive but to valorize their results.

5 PhD students finished their thesis.

The team leaders are regularly invited to international scientific meetings in viral hepatitis and hepatology and have a long-standing experience in organizing major international scientific meetings.

Thus, this very good publication, patent, presentation and conference record clearly documents the very good productivity of the team.

The partnerships are of the very good quality and include the excellent partners in the field. A productive collaboration with a Brazilian team has resulted in several publications and a patent application.

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

The impact of the research performed is important and of significant impact for the field as shown by the originality of the projects, the number and quality of the publications. A highly attractive point is the strength in translational research with initiation and direction of clinical trials incorporating concepts or tools developed in the unit and addressing treatment of hepatocellular carcinoma. This expertise is very important for the center and should be further developed.

The unit is well connected on a local, national and international level. These include interactions with the Lyon University Hospitals, the Cancer Center Léon Berard, national networks funded by the ANRS and INCA and international collaborations with other leading teams in the field.

The team leaders are regularly invited to give state-of-the-art lectures and serve as chairman at the leading international scientific meetings in viral hepatitis and hepatology. The team leader is member of the Editorial Board of Gastroenterology Clinic and Biology. One of the team members has been the president of the ANRS CSS7 (clinical hepatitis 2006-2010. Furthermore, the team has been organizing international meetings on viral hepatitis of the highest standard and has shown to attract the most brilliant speakers in the field (e. g. ISVHLD Meeting Paris 2006).

The team comprises both members of the Lyon University Hospitals (5 PU-PH, 4 PH, 2 MCU-PH) well as Inserm/CNRS research associates (4 CR Inserm/CNRS). The organigramm lists two postdocs and two PhDs. Recruitment of postdocs from abroad is planned.

Funding is good including support from ANRS, INCa (a multicenter grant coordinated by the team leader) and industry. The team participates in and co-cordinates several scientific and clinical networks.

The team is clearly the networking in translational research and clinical trials. The team leader has been and is coordinator of several clinical trials investigating novel molecules for the treatment of hepatocellular carcinoma. They have an outstanding reputation and a life-time experience in the treatment of viral hepatitis. The multicenter clinical trials directed by team members are highly original and “off the beaten track” (e. g. therapeutic vaccine for the treatment of HCV infection). The team leader is coordinator of a local scientific platform for hepatocytes funded by the Canceropôle and a large multicenter InCA project. Furthermore, the team is responsible for the Lyon viral hepatitis reference center. Multiple collaborations with foreign partners are listed. A very productive long-term collaboration includes a Brazilian lab (FIOCRUZ).

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

The scientific strategy is well described and addresses key questions in the field. The team leaders have made an effort on focus the projects on three axes which are interconnected. The organization and scientific animation is classical: one weekly lab meeting, one weekly department seminar, one weekly PhD/postdoc journal club.

The unit is well organized as shown by the efficient structure to monitor progress and solve technical and administrative problems. Internal and external communication is excellent

The coordination by the team leaders is very good and internal collaborations allow synergies which are in particular important for translation of research from bench to bedside. Risk taking is a important part of their strategy as illustrated by several highly innovative projects (e. g. novel models for HBV infection, the HCV therapeutic vaccine and the treatment of hepatocellular carcinoma).

Team leader and team members are Professors of Medicine at the University of Lyon and the team leader is Co-Director of the Liver Unit at the Lyon Hospitals. He has a very active responsibility in teaching undergraduate and graduate medical and PhD students as well as interns and residents at the hospital. All other principal investigators actively participate in the education of undergraduate students (M1, M2) and PhDs.

- Appreciation on the project

The very good and important impact of its research for hepatocarcinogenesis places this team well into the research cancer center. Hepatocellular carcinoma is a leading cause of cancer death world-wide and therapeutic options are very limited. Research is centered around three axes including (1) early steps of neoplasmic transformation of liver cells and interplays with viral infection, (2) HBV-induced hepatocarcinogenesis and a very original, important and strong translational axis comprising (3) clinical trials. The strongest project of basic research is the Wnt3, Fzd7 project. Another very strong project is the translational research in clinical trials: here cutting-edge projects are pursued – such as the therapeutic vaccine trial or novel approaches for the treatment of hepatocellular carcinoma such as radiotherapy.

The projects are original and will most likely advance the knowledge in the field. Risk taking is a important part of their strategy as illustrated by several highly innovative projects (e. g. novel models for HBV infection, HCV therapeutic vaccine, novel strategies for treatment of hepatocellular carcinoma).

- Conclusion

  – Overall appreciation

The very good and important impact of its research for hepatocacinogenesis places this team well into the cancer center. Hepatocellular carcinoma is a leading cause of cancer death world-wide and therapeutic options are very limited. Research is centered around three axes including (1) early steps of neoplasmic transformation of liver cells and interplays with viral infection, (2) HBV-induced hepatocarcinogenesis and a very original, important and strong translational axis comprising (3) clinical trials. Productivity and impact is very good as indicated by the quality and number of publications and its citations, number and quality of presentations, invited conferences and external funding.

The team is internationally recognized for its translational research in HCC and viral hepatitis. A major strength of the team is its translational research with original clinical trials where the team has an excellent track record and experience as indicated by the number and quality of trials and the leadership role played in these trials (as a PI or coordinator).

To further strengthen the team's long-term approach in basic science one may consider to focus on less projects and/or two major axes (one basic science axis, one clinical trial axis).

The translational and clinical projects are excellent and should be further developed including more resources.

The research addresses important questions in the field, is highly innovative and original and has a major impact for the understanding of the pathogenesis of and treatment of hepatocellular carcinoma as well as viral hepatitis.

  – Strengths and opportunities

A clear strength of the team is to have discovered Wnt3/Fzd7 as an important pathway in HCC pathogenesis and to have identified compounds with potential therapeutic implications.

Another major strength of the team is its translational research with original clinical trials where the team has an excellent track record and experience as indicated by the number and quality of trials and the leadership role played in these trials (as a PI or coordinator).

The impact of its research for hepatocarcinogenesis places this team well into the cancer center.

– Weaknesses and threats

Quite large number of basic science projects compared to the number of postdocs and students.

– Recommendations

Focus on less projects and/or two major axes (one basic science axis - e. g. further developing the Wnt3/Fzd7 project), one clinical trial axis).

Further develop the translational and clinical projects that are excellent.

E19 Team: Microenvironment, stem-cells and cancer

Team leader: Mrs. Véronique MAGUER-SATTA

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

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

- Relevance and originality of the research, quality and impact of the results

The main objectives of this young team (created in 2006) have been to understand how BMP and p53 families interfere in the Stem cell dialogue with their niche during appearance, maintenance, survival and resistance. The group was joined in 2007 and 2008 by researchers who brought new expertise. The major achievement is the discovery of the role of BMP-4 in megakaryocyte differentiation. The achievements are reasonable and should lead the team to establish a solid line of research if they are able to diversify their approaches and expand their goals. Nevertheless, competition is very strong in the field of stem cell and this is a major threat for this small team. Focus of this project is only on BMP4 and p53 pathways making this project somehow original but also certainly risky.

A total of 56 publications in peer-reviewed journals have been produced but not yet enough publications at good impact factor. During the last 5 years, the team leader has published 5 papers, including 1 article as first author in Exp Cell Res et 3 as last author in Leukemia, Blood and Curr Med Chem.

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

This team has an excellent complementarities of the different permanent staff and has a national/ international scientific recognition.

Three invited communications.

No recruitment of post-docs or scientist

Rare coordination of fundings (maybe Ligue contre le Cancer and ARC, not clear)

The team has a limited number of international collaborators with which they publish.

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

This team corresponds to the merging of researchers coming from E2 ad E16 under the supervision of a young researcher. The involvement in teaching activities is weak so far.

- Appreciation on the project

The projects aim at investigating the role of BMP and p53 family members by considering three major aspects: normal stem cell regulation by their niche, the role of tumor environment into cancer SC transformation and finally the mechanisms of cancer SC resistance. Investigating how microenvironment modulates SC cell fate through p53 and BMP pathways is very challenging. The attempt to characterize the role of the permanent dialogue between stem cells and their microenvironment in resistance and relapse is very pertinent .

The project is realistic and deals with a very and hot competitive subject, due to its impact in the field of oncology that could be exploited better in international context and for fund raising.

- Conclusion

  – Overall appreciation

This is a recently established team that has been able to make a number of relevant contributions. In the future, it should focus on engaging in new experimental approaches allowing internal collaborations and secure funding and group size to remain competitive. The main question of the group is challenging and is devoted to understand the relationship between microenvironment, stem cells and cancer. This may lead to the development of new clinical strategy specific of cancer stem cells as this constitutes one of the major clinical issues in the field of therapeutical oncology.

  – Strengths and opportunities

The group has clear objectives, It shares good collaborations with top-researchers in the field.

  – Weaknesses and threats

The group may be too small to maintain an international competitiveness in a long term. It has a low degree of integration with other researchers within the campus.

  – Recommendations

A diversification of experimental approaches would complement the current data.

The PI should improve his international visibility and try to raise international funding.

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: Apoptosis, cancer and development

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 2: Escape from failsafe programs and cellular 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+	A+	A+

Team 3: Senescent Escape Mechanisms

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	B	A	A+

Team 4: Epigenetic Alterations and Tumor Escape Mechanisms

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	B	B	B	C

Team 5: Endocrine differentiation: interactions with tumorigenesis and tumor progression

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 6: Role of TGF-beta in Pancreatic and Gastrointestinal Cancers

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	non noté	A+

Team 7: Early Molecular lesions in Oncogenesis

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	B	A	A	A

Team 8: Genetics of Breast 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 9: Alternative splicing and tumor progression

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 10: Nuclear domains and pathologies

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	B	B	A	B

Team 11: Estrogen signalling and breast 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 12: Signalling, Metabolism and Tumor Progression

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	B	B	A	A

Team 13: Therapeutic targeting of the tumor cells and of their immune environment

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 14: Innate Immunity Signalling and Oncogenesis

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 15: TGF-beta and Immune Evasion

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+	non noté	A+

Team 16: Mechanisms of chemoresistance to cytotoxic nucleoside analogues tubulin binding agents and therapeutic monoclonal antibodies

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 17: Mechanisms of chronic hepatitis B and C pathogenesis and novel antiviral strategies

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 18: Hepatocarcinogenesis and viral infection

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 19: Microenvironment, stem-cells 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	B	B	A	B

Université Claude Bernard Lyon 1

Le Président
Lionel Collet

Villeurbanne, le 15 Avril 2010

M. Pierre GLORIEUX
Directeur de la section des unités de l'AERES
20 rue Vivienne

75002 PARIS

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport du comité de visite concernant l'unité de recherche :

«Centre de Recherche en Cancérologie de Lyon » rattachée à mon établissement.

Le projet de Centre de Recherche en Cancérologie de Lyon, s'inscrit dans la dynamique suscitée par la création, à l'initiative de l'Université Lyon I, du réseau thématique de recherche et de soins «Synergie Lyon Cancer». Ce Centre de Recherche, dont les premiers contours ont été esquissés par le regroupement, au sein du Centre Léon Bérard et de la Faculté de médecine «Lyon Est», de plusieurs unités de recherche dont l'Université Lyon I est tutelle, est un élément central de notre politique de structuration de la recherche.

L'émergence de deux Centres de Recherche, en Neurosciences et en Cancérologie, associés au sein de la même Structure Fédérative de Recherche, est une étape décisive du développement des activités de recherche en Sciences de la Vie et de la Santé dans le cadre du PRES «Université de Lyon».

Je tiens par conséquent, à l'occasion de la venue du comité de visite de l'AERES, à réaffirmer mon total soutien à la création du Centre de Recherche en Cancérologie de Lyon.

Je vous prie de croire, Monsieur le Directeur, à l'expression de ma meilleure considération.

Le Président de l'Université

Lionel Collet

Centre Régional
Léon-Bérard
Soigner, chercher, vaincre. Ensemble

Lyon 1

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Lyon, April the 14th

Dear Madam, Sir

Please find enclosed our answer to the evaluation report performed by the AERES committee regarding the new Cancer Research Center we wish to establish.

I would like to express our thanks to the AERES committee for the impressive work they performed, and for the positive feedback and comments they gave us to improve our projects, both at the level of the general organization of the Center and of the teams' projects.

You will first find in the following pages the answer regarding the general evaluation of the Center (page 2), followed by specific comments by each of the applying 19 teams (pages 3-12).

We thank you in advance for your consideration and we are looking forward to hearing from you soon,

Best regards,

Pr. Alain PUISIEUX

OVERALL EVALUATION OF THE CANCER RESEARCH CENTER

The Direction of the Lyon – Cancer Research Center wishes to thank the AERES committee for their positive feedback and relevant advice they gave us on this new project. We were pleased to see that the AERES committee recognized the ambition of this new structure that aims at establishing a center of excellence to promote cancer research, medical transfer and training and education.

The committee made very useful and relevant recommendations to the Cancer Center, with which we are in complete agreement, i.e. set-up an oncology training program, develop technological platforms, create an administrative unit. These key points were indeed addressed in the written project and also during the oral presentations during the committee visit, as they are major elements for the success of the Center and that they will bring add-values to our staff members. In a very brief summary:

- We will develop in the next four years our own **master's program in oncology**, based on a critical mass of 89 permanent scientists, professors and assistant professors. In terms of deliverable, we will submit to the University in 2013 the proposal of this new training program, for an official launch in 2015.
- In addition, it is essential that the Center has to develop and implement **technological platforms**. For instance, teams of the Center wrote a grant proposal in March 2010 to apply for a medium-size equipment joint call. If accepted, this equipment will re-enforce our imaging core-facilities. We also wish to think over the development of our platforms in the perspective of the current structuration of the SFR Lyon-Est.
- Finally, it is definitely our priority to establish an **administrative unit** in the next couple of months. As such, the Inserm recently accepted to support the general secretary position and a suitable candidate is currently being recruited. This is of course a first step towards a further development of this administrative unit in the near future, as presented in details in the written and oral presentations of the Center.

In conclusion, we thank again the AERES committee for their advice and their constructive remarks that will clearly help us to improve the development and the implementation of our project.

TEAM E1 "Apoptosis, cancer and development"
Team leader: Patrick Mehlen

The E1 team leader is thanking the committee members for their kind evaluation. The E1 team leader is willing to answer the specific comment on "weaknesses/threats":
"It is a very large group. The direction of a large group together with all the activities of the team leader may become a tour de force if not relying on "subgroups leaders" who are not identified. This could be a potential problem."

The E1 team (and the existing CNRS UMR5238) is indeed a « monothematic » group which studies the dependence receptor notion. However, it is divided in several « subgroups » that were actually presented during the AERES interview. These 4 subgroups are headed by faculties (CNRS, INSERM, or university Professor). The first subgroup, leaded by Agnès Bernet, professor at University of Lyon, IUF, is developing the netrin-1 dependence receptors, the second subgroup, headed by Servane Tauszig-Delamazure, CR1 CNRS HDR, is developing tyrosine kinase dependence receptors, the third subgroup is headed by the PI himself on other dependence receptors and the last subgroup is headed by Jean-Guy Delcros, a CR1 INSERM HDR, pharmacologist, who is in charged of the preclinical transfer of the team.

TEAM E2 "Escape from failsafe programs and cellular plasticity"
Team leaders: Alain Puisieux and Stéphane Ansieau

We thank the AERES committee for their very positive evaluation. We just would like to correct the number of invitations to scientific events: 13 invitations since 2005 (and not 6 as mentioned in the report) to international and national meetings (see details below) and 19 invitations to international and national seminars.

Invited speakers to scientific meetings since 2005

- Puisieux A. Consortium's International Symposium « Tumor Stem Cells: promises and controversies ». Ulm, Allemagne, 2010.
- Puisieux A. « Reactivation of EMT-inducing transcription factors and cancer development» 10th International Conference on Cancer-induced bone disease. Sheffield, Grande-Bretagne, 2010.
- Ansieau S. Journée Scientifique EMT, Paris, 2010.
- Puisieux A. 100th Annual Meeting of the American Association for Cancer Research, Denver, USA, 2009.
- Puisieux A. Key note lecture, Eurocancer 2009, Paris, 2009.
- Ansieau S. 4ème EMT meeting, Tucson, USA, 2009.
- Puisieux A. Académie Nationale de Médecine et Pharmacie, Paris, 2009.
- Puisieux A. Journées du Cancéropôle Archamps, 2009.
- Puisieux A. 8th International conference of anticancer research, Kos, Greece, 2008.
- Puisieux A. p53 workshop IARC, Lyon, 2007.
- Puisieux A. 2ème Rencontres Alpines d'Oncologie, Courchevel, France, 2006.
- Puisieux A. Children's Oncology Group Meeting Dallas, USA, 2005.
- Puisieux A. 12ème Congrès du Club Hématopoïèse et Oncogenèse, Presqu'île de Giens, 2005.

Finally, we fully agree with the AERES committee's recommendation that we should increase the hosting of foreign students and scientists. Note nevertheless that we do host a US post-doctoral researcher, George Hinkal (since 2008), and that five ERASMUS masters students in Pharmacy

stayed 4-5 months in our lab, between 2005 and 2009 (3 from Belgium, one from Italy and one from Malta).

TEAM E3 "Senescent escape mechanisms"
Team leader: David Bernard

We thank the AERES committee for the evaluation of the team. We will of course take into account the recommendations of the committee. We would like to give additional information concerning the size of the team. The team is now composed of the group leader, 2 postdoctoral scientists, 1 PhD student, and one M2R student that will apply to be a PhD student. A third postdoctoral scientist will be recruited after the summer through a Centre Léon Bérard support.

TEAM E4 "Epigenetic Alterations and Tumor Escape Mechanisms"
Team leader: M. Robert DANTE

Factuals
"Three publications are listed as a first or last author from members of the group. The group has produced roughly one paper each year in a good international journal (Oncogene, NAR). (Information was taken from the IF of the team leader because it ***is missing in the printed report from group 4 (Bilan, pp 93-106****), in particular the two reported publications with IF>20 were not found). Good publications, some in collaboration with a group leader in the field of epigenetics"*

It is worth mentioning that the team number in the project (E4) is similar to its team number in the scientific report (BILAN): my group was indeed part of the team 4, with C. Dumontet as a PI, within the Inserm U590 unit. This homonymy seems to have led, despite the explanations given during the visit, to a certain confusion in the appreciation of the results and compromised the credibility of the whole project.

The list of publications 2004-2009 corresponds, as indicated in the project, to the production of the whole group « **Publications 2004-09: 39 (IF>4), 14: IF>6; 5: IF>9; 2: IF>20".**
For the 2 IF>20 not found by the experts:

Weber W, Rimann M, Spielmann M, Keller B, **Daoud-El Baba M**, Aubel D, Weber CC, Fussenegger M. Nat Biotechnol. 2004 Nov; 22(11):1440-4. Kramer BP, Viretta AU, **Daoud-El-Baba M**, Aubel D, Weber W, Fussenegger M. Nat Biotechnol. 2004 Jul;22(7):867-70.

M. Daoud-El Baba has well-recognized expertise in pharmacological treatments of mice and has just get a paper published in Nat Biotechnol : Kemmer C, Gitzinger M, **Daoud-El Baba M**, Djonov V, Stelling J, Fussenegger M. Nat Biotechnol. 2010 Mar 28.

If we take, as a reference, the list of publications 2005-2009 validated by INSERM: 39 publications, 19 (IF>5). 9 listed as a first or last author from members of the group.

"It seems that the team has difficulty to recruit post doc and students".

This statement probably comes from the problem mentioned above: 3 students (director of research RD) have obtained their PhD *summa cum laude*, 2 have post-doctoral position, 1 has a permanent position in IUT lyon1. M Peretti did a post-doctoral stay (CEA grant, RD) from December 2005 to July 2006 in RD group. Currently 2 students (M2 and PhD) work in the group, the arrival of additional students is planned for this autumn and post-doctoral grant applications are under evaluation.

"A collaboration with a top researcher in the epigenetic field led to joint papers; no information is given regarding the continuation of this joined work."

This point has not been raised during the visit. However, this collaboration is still active, and collaborative paper has been published at the beginning of the year: Chatagnon A, Ballestar E, Esteller M, Dante R. A role for methyl-CpG binding domain protein 2 in the modulation of the estrogen response of pS2/TFF1 gene. PLoS One. 2010 Mar 12;5(3):e9665. Currently, the collaborative program with M. Esteller group (PEBC-ICO-IDIBELL, Barcelona) is focused on the involvement of the Methyl-CpG binding domain proteins in the control of miRNA in cancer cells.

Appreciation on the project and Recommendations.
"The committee has doubt about the competitiveness of the group without additional expertise for example recruitment of other teams working on epigenetic modifications."
As mentioned in the "appreciation of the project section" The project is well structured and is backed by high quality platforms (Platform IBISA "functional genomic and high throughput sequencing)". *RD has a well-recognized expertise in epigenetics, and he is in connection with many scientific outside France, for example he was a founding member (1994) of the DNA Methylation Society, now called Epigenetics Society.*

Interactions with other groups:
a) D. Bernard (E3) and P. Mehlen (E1) in collaboration with E4 analyze the impacts of epignetics modifications on candidate genes. b) Jean-Yves SCOAZEC group (E5) have published several papers on DNA methylation and gene expression, 2 of them in collaboration with E4 team (RD and J lachuer). The analysis of candidate genes by pyrosequencing is currently developed in the Pathology unit (Dir. Prof JY Scoazec) in Hospices Civils de Lyon.

Integration in the global project of the Research Center:
a) Genome-wide analysis of epigenetic modifications, developed by the team E4, provide an important data bank for other groups, since the models analyzed are also used by many teams of the Research Center.
b) Moreover, this program is establishing strategies and techniques necessary for global analyses, which are now integral part of competitive researches. Indeed, methods used: microarrays analysis (transcriptomic, ChIP-chip), high-throughput sequencing (ChIP-Seq, massive sequencing), are absolutely necessary for "epigenetic programs", but are not limited to this field.

In conclusion, due to its specific expertise in epigenetics, the E4 provides added values to the other teams.

TEAM E5 "Endocrine differentiation: interactions with tumorigenesis and tumor progression"
Team leaders: Jean-Yves Scoazec and Chang-Xian Zhang

We thank the committee for its thoroughful and detailed analysis of our project. We would like to offer the following comments on some points and issues raised in the report.

1. Numerous papers have been published around the three topics previously developed including 2 Gastroenterology, 1 PNAS and 1 Oncogene. The IF of others do not exceed 5.
As stated in the original document, the total number of publications authored by one or several members of the new team in journals with IF>5 is: 31 (9 from original group (a), 9 from original group (b), 12 from original group (c)), including 15 with one member of the team as first and/or last author. Journals of publication are: PNAS (2), Gastroenterology (3), Hepatology (1), Mol Cell Biol

(1), Plos Genet (1), Hum Mol Genet (1), Nucl Acids Res (1), Oncogene (2), Cancer Res (1), Carcinogenesis (2), Endocrine-Related Cancer (5), J Clin Endocrinol Metab (8), J Nucl Med (3).

To the AERES comment: *"Of note, one of the team members signed 10 publications alone in the quadrennial with no apparent link with the team. Is there a planned integration in the new team?"*
As for subgroup (b), the team member who signed 10 papers in the last quadriennal is clearly a member of the future team.

2. A whole INSERM unit is incorporated into the team.
As stated in the report, the new team is made from members coming from three different previous research units (2 INSERM, U865 and U667, 1 CNRS, UMR5201). We would like to stress that not all the members of the previous U865 will be included in the future team: only two of the previous 6 full time researchers will belong to the future team, as well as only two of the previous HU researchers. As a result, the composition of the future team will be rather equilibrated between the various units of origin.

3. At least 10 distinct objectives are defined in the proposal! Although an important effort was made to integrate the fusion of the three groups, this results in a sometime imprecise description of the future projects.
As stated in our application and as acknowledged in a previous paragraph of the AERES report, our project is clearly organized along three main themes. Each of these themes has been presented as addressing a limited number of questions, which are closely related, complementary, and usually based on ongoing projects (which warrants their feasibility).

TEAM E6 "Role of TGFb in Pancreatic and Gastrointestinal Cancers"
Team leader: Laurent Bartholin

We would like to thank the committee members for the time they spent to evaluate our work. As recommended, we will be vigilant to maintain an adequacy between the size of our group, the number of mouse models we develop and the funding we raise. To strengthen our team, a new postdoctoral fellow will join the group (Johann GOUT) by the end of the month (Inserm fellowship). Therefore, there will be two postdocs in our team (not 1, as mentioned in the table in N3).

TEAM E7 "Early molecular alterations during oncogenesis"
Team leader: Serge Manié

We agree with the conclusions of the report. We are actively pursuing our effort to increase manpower and funding in order to consolidate the foundation of our team.

TEAM E8 "Genetics of breast cancer"
Team leader: Sylvie Mazoyer

We thank the committee members for their evaluation of our team. The only point that we would like to stress is that the FTE of the team has been overestimated (+ 3 FTE) due to errors in the table reporting team staff (see the correction file).

Note that there is a mistake in the report we submitted to the AERES concerning the date of arrival in the team of one of the EPST researcher: we wrote 11/1995 instead of 06/2008. As a result, the "in

the report" N2 number in the table depicted in "Team staff" section, should be 2, not 3. The "in the report" and "in the project" N3 numbers should read 1, not 2. The "in the report" N4 number should read 1, not 2.

TEAM E9 "Alternative splicing and tumor progression"
Team leader: Didier Auboeuf

We are grateful to the AERES experts for their positive comments on our team's work.

We would like to emphasize that, in addition to one full-time INSERM researcher, the team includes two PhD students, two engineers in short-term contract, one post-doc and one researcher who holds a "Jeune chercheur confirmé" contract from Inserm and is applying for a permanent position.

We would like to bring to the attention of the committee 4 recent publications which had not been mentioned in the written document:

1. Exon-based clustering of murine breast tumor transcriptomes reveals alternative exons whose expression is associated with metastasis. Dutertre M, Lacroix-Triki M, Driouch K, de la Grange P, Gratadou L, Beck S, Millevoi S, Tazi J, Lidereau R, Vagner S, Auboeuf D. Cancer Res. 2010 Feb 1;70(3):896-905. PMID: 20103641
2. Splicing factor and exon profiling across human tissues. de la Grange P, Gratadou L, Delord M, Dutertre M, Auboeuf D. Nucleic Acids Res. 2010 Jan 27. PMID: 20110256
3. NFAT3 transcription factor inhibits breast cancer cell motility by targeting the Lipocalin 2 gene. Fougère M, Gaudineau B, Barbier J, Guaddachi F, Feugeas JP, Auboeuf D, Jauliac S. Oncogene. 2010 Jan 25. PMID: 20101218
4. Estrogen regulation and physiopathologic significance of alternative promoters in breast cancer. DutertreM, Gratadou L, Dardenne E, Germann S, Lidereau R, Driouch K, de la Grange P, Auboeuf D. Cancer Res. 2010 (IN PRESS)

TEAM E10 "Nuclear domains and pathologies"
Team leader: Jean-Jacques Diaz

We would like to express our appreciation to the committee for their recommendations.

I – Corrections (referring to p29-31 of the report of the committee)

i) In reference to point # N3. (Form 2.2: the number of other professors and researchers) is 0 (not 1).
ii) The planned team will include 5 FTE (not 4): 1 DR2 INSERM, 1 CR1 INSERM, 1 CR2 CNRS, 1 MCU UCBL, 1 PU/PH UCBL. The 1.8 FTE technician (1 IE CNRS and 0.8 TR UCBL) have permanent positions (not "non permanent")

II – Comments

Addressing concerns of the committee regarding the involvement of the team in international network and collaborations, we provide the following information which was omitted in the written document.

- The leader and members of the future team have been invited to deliver lectures in recognized international meetings (Siena proteomic meetings 2009, European Worm Meeting 2009, New Orleans Digestive Disease Week 2010). They have co-organized international meetings

(*C.elegans* European Worm Meeting, Spain, 2008; International congress on capsule endoscopy, Spain, 2008).

- The team leader is Executive Editor of Journal of Proteomics since its creation in 2007.
- The team was the French partner of the integrated FP6 European project PROPHECY and coauthored several publications resulting from this project (Greco *et al*. Infect Disord Drug Targets. 2007 ; Juban *et al*. Callé *et al*. J Virol 2008; Mol Cell Biol 2009; Belin *et al*. RNA 2010).). The team is actively involved in building up European networks through projects currently under examination (FP7, Dundee, Moscow, Prague, Geneva).
- The team has track records of joint publications with international teams. Three publications in 2010 document continuation of this strategy: (Hacot *et al*. Curr Prot Mol Biol. 2010 in press; Vidal *et al*. Mol Cancer Res. 2010; Catez & Hock. Biochem Biophys Acta. 2010

Finally, concerns of the committee regarding demonstration of cohesive research between team members may be dampen by noting that members of the team have coauthored joint publications (Diaz/Catez, Diaz/Mertani, Diaz/Saurin), have co inventors of the same patents (Diaz/Saurin) and share common grant funding (Diaz/Mertani; Diaz/Saurin).

TEAM E11 "Estrogen signalling and breast cancer"
Team leader: Laura Corbo

We thank the evaluation committee for its thorough and constructive report regarding our team.
We provide additional information related to some specific comments or recommendations.

a) "*The use of cell lines may introduce bias, the study of tumor samples is too limited and should be developed."*
One objective of our project is to study the molecular mechanisms involved in resistance to a recently introduced treatment of hormone-dependent breast cancers based on the use of aromatase inhibitors (AI). Breast tumour samples collected from patients who relapsed under AI therapy are not yet currently available. We are striving to collect them. Thus, for the moment, the project takes advantage of the use of four new cellular models of in vitro acquired resistance to aromatase inhibitors . We are aware of possible biases attached to the use of these cell lines. We believe that studies of these cell lines may provide model mechanisms of AI resistance which will then be carefully evaluated for their clinical relevance on samples collected from patients.

b) "*A mouse knock-in model is being generated to address the physiological relevance of ERalpha methylation by PRMT1. This part of the project is ambitious and risk-taking.* "
We fully agree with the committee that this project is ambitious and risk-taking. It has been initiated and is being actively developed in collaboration with Prof. Chambon's laboratory, recognized expert in the field of hormone signaling and mouse models.

c) "*The leadership of the various projects is not clear. The connection between the different subgroups (basic versus applied projects) has to be improved."*
We apologize for the lack of information about the scientific organization of the team. Our research program is based on a collaborative and complementary partnership between the team leader (Laura Corbo, two senior basic scientists, Muriel Le Romancer, with experience in estrogens signalling pathways and protein post-translation modifications, and Pascale Cohen with expertise in the field of hormonal resistance and genomics-based methodologies. In addition, the presence in the team of Isabelle Treilleux, MD PhD, from the Pathology department of the Léon Bérard Cancer Center, permits a direct evaluation of the clinical relevance of our basic research results. Depending on the nature of specific projects, the leadership is endorsed by one of these investigators.

TEAM E12 "Signalling, metabolism and tumor progression"
Team leaders: Ruth Rimokh and Germain Gillet

First we would like to thank the committee for its constructive recommendations and its appreciation of the rationale for the merging of our two, previously independent research groups.

Taking into account concerns expressed by the committee, we provide the following specific information:

- Financial support: over the last 4 years, the merged budget of the two teams was around 250 K€ per year for 5.5 FTE investigators, and included several grants larger than 100 K€ (Région Rhône-Alpes : 150 K€ ; ARC : 350K€ , INCa: 395 K€, LNCC 129 K€). We also benefitted from industrial support (Diamed, Genzyme) for a total of 222 K€ over the last four years which is planned be renewed for the next coming three years. Of note, the associated industrial contracts, resulted in delaying publication of significant results in order to secure IP. Presently two manuscripts describing these results are submitted for publication.
- Scientific production: Actually three patents mentioned in the written document have been deposited (2005, 2007, 2008) although a single patent was stated in the report of the committee. Also, since the initial document was submitted to the committee (September 2009), two new articles of the team with coauthors from Spain and Canada respectively have been published (PLoS One, 2010; BMC Cancer, 2010).
- TGF-b signalling is actively being investigated by several teams from the research center thus providing fruitful collaborations. Collaborations with teams E6 and E15 have resulted in 3 recent publications (Genesis, 2008; Plos Genet, 2009; J Exp Med, 2009). One grant involving teams E5, E6, E12 and E15 is ongoing (INCa, R. Rimokh scientific coordinator). It may be worth mentioning that the leader of team E6 was trained by Ruth Rimokh.
- Indeed the Smad4/Tiff1g project lies in a competitive field. Our team focusses on *in vivo* approaches using the mouse model (collaboration with R. Losson's lab, Strasbourg). It has already provided convincing evidence for a major role of TIF1g in the maturation of lacteal ducts in the mammary gland. These observations are presently being written for publication.
- Our current strategy for the project on EMT inhibitors is in accordance with the suggestions from the committee. Our focussed approach on new targets has already led to the identification of 3 original leads which all participate in metabolic regulations.
- We also concur with the committee that *« The role of metabolic tumour cell adaptation in the EMT process is very original and a poorly explored concept »*). We address this question taking advantage of the know-how of P. Gonzalo in mitochondria bioenergetics gained during his post-doc and of t the High Field NMR Center (CRMN) at University Lyon I, a unique facility providing a strategic advantage for developing metabolomic projects.

TEAM E13 "Therapeutic targeting of the tumor and of its immune environment"
Team leaders: Christophe Caux and Jean-Yves Blay

We thank the board of reviewers for their time and consideration in analysing our project. We have carefully considered and analyzed their overall evaluation which is going to be useful for our future scientific strategy. We acknowledge, as pointed by the reviewers, that although a pertinent mix of basic and clinical research, our program is certainly planning to address too large number of transversal questions. As recommended by the reviewers, we will take advantage of the year 2010

to prioritize emerging questions in the aim to focus on the most original approaches and to increase our competitiveness.

TEAM E14 "Innate immunity signalling and oncogenesis"
Team leader: Toufic RENNO

The team leadership totally concurs with the conclusions of the report and with its recommendation that a full-time researcher be recruited in order to improve the critical mass and visibility of the team.

TEAM E15 "TGF-beta and Immune Evasion"
Team leader: Julien Marie

We have read carefully comments on both the Center and Team E15 and we thank the referees for recognizing the recent discovery of team E15 on the "*role of TGF-beta in autoimmune development in mice*" as one the four "*most promising discoveries of the Center*".

We agree that the small size of a group can be regarded as "*a weakness*", however we would like to remind to the referees that Team E15 is very young since it just got its official independency by Inserm in January 2010 with an ATIP/AVENIR label. As exposed during the oral presentation, the team will be enriched from May 2010 by both another post-doc and another full time senior researcher (CR2 Inserm). Moreover we would like to mention that there are several miss-transpositions from the submitted file to AERES on the table of the evaluation file page 40:

- N3 (future): the number of Post-Docs is 2, not 0
- N6 (future): the number of PhD students is 1, not 0

In this regard, from May 2010, Team E15 will be composed of 2 post-docs (from USA and Ireland), 1 PhD student, 2 technicians and 2 full time senior researchers, and we believe that the comments on "*the extremely limited size of the team and the lack of full time senior researchers*" could be moderated as well the lack of attractiveness of the team at the international level. Considering the information above and the fact that with a size of 5 people, the young team managed to publish several papers in high impact factor journals (Immunity, J.Exp. Med.) and got a prestigious international grant in the last couple of years.

We appreciate that the referees regarded our collaborations as fruitful and stable however, we have noticed several non-correct information.
On the one hand, some collaborations, no mentioned neither in the written document nor during the oral presentation, have been assigned to the team and on the other hand several national and international collaborations have been occulted. Team E15 has never collaborated with the NCI, or UCSF. However team E15 collaborates with several international groups in the USA (University of Washington, Seattle, University of Ohio Cleveland, NYU, University of Virginia, Charlottesville…), in Asia (University of Malya, Kula Lumpur), in Europe, London, Cologne, and several national groups mainly Inserm groups in Paris.

Finally, we would like to remind that the project of team E15 is not "*to discriminate which cells of the immune system could be the main target cells of TGF-b regulatory effects*", since the team has already addressed this question (Immunity 2006, and J. Exp.Med 2009).

TEAM E16 “Anticancer antibodies”
Team leader: Charles Dumontet

We agree with the committee’s suggestion that a priority is to recruit senior researchers in order to strengthen the permanent staff. The team also has several brilliant young candidates who are currently seeking tenure.

The group is keenly aware of the rapidly increasing competitivity in the field of monoclonal antibodies and will thus strive to excel in specific aspects of this field, in particular characterization of accessory cell function, preclinical modeling and translational research.

Team E17 “Mechanisms of chronic hepatitis B and C pathogenesis and novel antiviral strategies”
Team leaders: Fabien Zoulim and Lucyna Cova

We thank the AERES committee for its constructive comments and recommendations.

Note that the team has 3 engineers and technicians with a tenured position. Furthermore, 2 administrative staff with a tenured position are shared with Team E18. The total number of engineers, technicians and administrative staff with a tenured position should therefore be 4 for team E17 (instead of 2).

TEAM E18 “Hepatocarcinogenesis and viral infection”
Team leaders: Philippe Merle and Isabelle Chemin

We thank the committee for its positive evaluation and appreciation of both fundamental and translation research axis of our team. Our research topics are aimed to better understand early events leading to the development of hepatocellularcinoma and possibly prevent its appearance. We would like to underline the fact that PhD students that will finish this year (2/7) will be replaced by new PhD students (several M2 are in the team this year) and also that new post-docs already arrived or will be involved in the projects in the next 4 years. We may not be have been clear enough and this is of importance regarding the different topics in our team and the number of persons involved (7 senior scientists). As suggested by the committee, our team is planning to focus as far as possible on its main objectives.

TEAM E19 “Microenvironment, stem cells and cancer: role of p53 and BMP families”
Team leader: Véronique Maguer-Satta

We are grateful to the AERES visiting committee for their positive feedback and very helpful comments that will certainly help us to improve our team project.

Corrections to be noted: Some mistakes appeared in team composition in the table:
N3: should be 3 instead of 2
N4 and N5: all our technical staff benefit from a permanent (tenured) position and therefore the number in N4 should be 3 instead of 2 and in N5 should be 0 instead of 1.
N6: The number of PhD students in 2011 will be 3 plus 2 (currently in M2 and if financing is achieved). N6 should be 5 instead of 3. N7: should be 4 instead of 3

Commentaries.
- Team size: We are currently participating in 2 INCA grants under evaluation (after positive pre-selection) in which we asked for post-doctoral positions. In addition we are determinate to shortly recruit a new researcher (CR) to reinforce our permanent staff.

- Teaching activities: We have a researcher with teaching duties that ensure a total of 240h per year (instead of 192h/y required). The two full time researchers are involved each year in both local (Master teaching) and national (Ecole de Formation Européenne en Cancerologie-EFEC) teaching activities.

Project: The committee recommends enlarging our experimental approaches. In that regards we have started other approaches:

- In the hematopoietic system, we are currently involved in a new project conducted by Pr Jean-Michel Dubernard and Pr Mauricette Michallet (Edouard Herriot Hospital, Lyon). This project aims to create an IHU (Institute Hospital-University) to challenge the understanding of the role of hematopoietic stem cells in graft process (homing and tolerance). Regarding our expertise, we were invited to participate in the context of double cord graft for leukemic patients.
- In the mammary system. We collaborate with Dr Annick Harrel Bellan (Institute André Lwoff, Villejuif) to investigate miRNA expression (using arrays) and with Dr Mina Bissell (Lawrence Berkeley) to apply a new large screen technique she developed to analyze the breast environment effect onto stem cells populations that we just identified and characterized (Stem Cells, *under review*). In the context of an INCA project with Pr Richard Iggo (Institut Bergonié, Bordeaux), we will identify by large screening approach bio-peptides involved in mammary stem cell fate. Furthermore through access to the large European biobank (EORTC 10994 trial) we will be able to largely screen for the expression of factors of interest within different subtypes of breast tumors.

Weakness and threats:

- We would like to apologize on the lack of clarity on internal interactions of our team with others teams within the center that persist after our presentation as noted by the committee. Indeed, we collaborate on our projects with teams E2 (Twist-1 and CML, Blood *in positive revision*), E13 (breast cancer environment), E14 (p53 and β-catenin), E16 (stem cell resistance) and E18 (p73 and hepatic stem cells). We are involved with team E5, E17 and E18 in a collaborative human primary Hepatocyte platform (PROCAN 2008) with other partners to support an INCA project on hepatocarcinogenesis that associates these teams (PAIR-CHC 2009). We will also be the leader in setting a new and original platform to construct human 3D microenvironment models in association with E13 and in collaboration with E2, E14, E16 and E18.
- We agree that the international visibility of the PI is an important issue that suffers in the past from the fact that its professional activity was interrupted for almost a 2 year period (end 2004-2007) for familial major reasons. Now based on the PI close interaction with top-researcher in the stem cell field (as noted by the committee) this is likely to increase within the next years.
- We agree with the committee comments that it will be important in the close future to recruit new scientists to expand our young team.