ETIC - Signalisation normale et pathologique : de l'embryon aux thérapies innovantes des cancers

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Normal and pathological signaling from the embryo to the innovative therapy of cancer

ETIC

Under the supervision of the following institutionsand research bodies:

Institut Curie

Centre National de la Recherche Scientifique - CNRS

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

Université Paris-Sud

February 2014

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

Department for the evaluation of research units

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

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

On behalf of the expert committee,

- Mr. Marc BILLAUD, chair of the committee

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

Evaluation report

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

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

Unit name:	Normal and pathological signaling: from the embryo to the innovative therapy of cancers
Unit acronym:	ETIC
Label requested:	UMR CNRS, U INSERM
Present no.:	UMR 3347 – U 1021
Name of Director (2013-2014):	Mr Simon SAULE
Name of Project Leader (2015-2019):	Mr Simon SAULE

Expert committee members

Chair:

Mr Marc BILLAUD, Institut Albert Bonniot, Grenoble

Experts:

Mr Laurent BARTHOLIN, Centre de Recherche en Cancérologie de Lyon

Ms Dorothy BENNETT, Saint Georges University, London, United Kingdom

Ms Agnes BERNET, Centre de Recherche en Cancérologie de Lyon (representative of CNU)

Mr Olivier CUVILLIER, Insitut de Pharmacologie et de Biologie Structurale, Toulouse (representative of CoNRS)

Ms Heather ETCHEVERS, INSERM, Marseille

Ms Cécile ROCHETTE-EGLY, IGBMC, Illkirch (representative of CSS INSERM)

Mr Bernard SALLES, UMR Toxalim, Toulouse

Mr Massimo SANTORO, Medicina Molecolare e Biotecnologie Mediche, Napoli, Italy

Scientific delegate representing the AERES:

Mr Pierre COUBLE

Representatives of the unit's supervising institutions and bodies:

Ms Geneviève ALMOUZNI, Institut Curie

Mr Etienne AUGE, Université Paris 11

Mr Thierry GRANGE, CNRS

Ms Anne ROCHAT, INSERM

1 • Introduction

History and geographical location of the unit

The unit entitled ETIC (from Embryo to Innovative Therapy in Cancer) was created in January 2010 and is a joint research Unit that depends on the Institut Curie, the CNRS (UMR 3347), the INSERM (U 1201) and the Université Paris-Sud. The ETIC is located on the Campus of Université d'Orsay and has 540 m^2 of laboratory space at its disposal. The staff comprises 67 persons and the unit is organized in 5 independent teams. During the past contract, two of the present teams were merged since they did not have the critical mass to constitute two independent groups. Because they have reinforced their internal structure with the arrival of new staff members, both team leaders apply again for the creation of two independent groups. Furthermore, a young investigator, who leads an ATIP/AVENIR team is going to join the unit for the forthcoming contract. Overall, seven groups should constitute the ETIC unit for the next 5-year contract.

The Intitut Curie provides equipments and platforms to its units and this high profile technical infrastructure is a resource that creates outstanding conditions for the development of innovative research projects. On the Orsay site, the ETIC teams have access to the Imaging facility, the Radexp (experimental radiotherapy), the 2D/3D structural and chemical imaging and the histology platforms as well as the flow cytometry core facility and the in vivo experiments platforms including mouse, Xenopus, and zebrafish facilities.

Management team

The current director of ETIC (PR1 at Université Paris-Sud) and the deputy director (DR1 at INSERM) apply for renewal of their mandate for this 5-year contract. The director is in charge of the organization of the unit and he oversees the administrative management of the laboratory. He is assisted in his decisions on the scientific strategy by a board of principal investigators (PIs) that includes the team leaders and meets occasionally when pressing questions have to be discussed.

AERES nomenclature

SVE1, LS3

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	6	8
N2: Permanent researchers from Institutions and similar positions	9	12
N3: Other permanent staff (without research duties)	12	11
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	8	7
N6: Other contractual staff (without research duties)	7	6
TOTAL N1 to N6	**42**	**44**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	14	
Theses defended	12	
Postdoctoral students having spent at least 12 months in the unit*	7	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	11	11

2 • Overall assessment of the interdisciplinary unit

Overall, the research developed at ETIC is considered as good to outstanding. The experts committee has favorably evaluated the innovative quality of the research programs, the leadership of the team leaders and the dense networks of internal and external collaborations that have been woven. The unit integrates research programs that go from the investigation of basic mechanisms of embryonic development, mostly focused on the neural crest (NC), to the exploration of the genetic and biological bases of melanoma and medulloblastoma cancers arising from subpopulation of neuroepithelial cells. This is a coherent frame of interlinked research themes that concentrates expertise in embryology, genetics, cell signalling and translational research. The experts committee has also appreciated the active participation of the ETIC teams in the structuration of local programs (Programme Incitatif et Collaboratif Institut Curie, Labex) and their fruitful collaborations with clinical departments of the Institut Curie. The arrival of an ATIP/AVENIR team led by a young investigator working on medulloblastoma will reinforce the dynamics of the research of the laboratory on the mechanims of cell signaling associated with tumor development and will offer novel opportunities for internal collaborations.

However, even if the evaluation is positive, the experts committee has raised several points of concern. First, the distribution of the ITA/BIATSS (technical) personnel is unbalanced among the teams and this situation limits the research capability of the groups deprived of technical support. Second, the experts committee has noted that no CR (permanent staff researchers) have been recruited at the CNRS or INSERM since January 2010, thus indicating that the unit's appeal may not be optimal to attract successful post-docs with strong track records. However, it must also be taken into consideration that two MCU (assistant professors) have been recruited during this period. Third, the relative limitation of the laboratory and office spaces constrains the evolution of the teams and their capacity to hire more personnel. Fourth, circumscribed concerns have been raised about the innovative and competitiveness aspects of certain research projects.

Strengths and opportunities related to the context

The overall quality of the scientific production of ETIC is good to first-rate.

Although there is heterogeneity among the groups, ETIC teams are nationally and internationally renowned for their research and they are directed by scientists with strong leadership capacities.

The strategic vision is coherent with the determination of research axes that logically integrate complementary projects to tackle fundamental questions on the ontogeny of the NC, the identification of cell signalling processes derailed in NC-derived melanoma as well as in medulloblastoma and on translational research issues that aim at assessing novel agents that sensitize tumor cells to radiotherapy and chemotherapy.

The recruitment of an ATIP/AVENIR group that is going to join ETIC in the frame of the new contract will strengthen the scientific dynamics of the unit.

The interactions between ETIC teams and the clinicians of the Institut Curie are active. The unit is also well integrated in local scientific programs (PIC: programme incitatif et collaboratif Institut Curie, Labex CellTisPhysBio) and most of the teams are associated with international collaborative networks.

A tangible involvement in translational research should be noted with the creation in 2006 of the startup "DNA therapeutics" by one of the group leaders; the scientific bonds between the team and the biotech have been maintained. Also, industrial contracts with the private sector (Chanel, Sanofi) have been negotiated.

Patent activity and technlogy transfert are adequate for a unit of this size since six patents have been filed during the past contract

The fund raising at a national level is highly competitive.

Weaknesses and threats related to the context

The distribution of the ITA/BIATSS personnel is unbalanced among the teams.

The unit has to cope with a limitation of laboratory and office spaces that restricts the proper evolution of the groups and confronts the personel of the unit with working conditions that are not completely appropriate, introducing unnecessary frictions.

The attractiveness of the teams for post-docs with excellent track-records who could be eligible for a position at CNRS or INSERM could be enhanced.

Grant applications at an international level should be prioritized, for example with European Community sources (ERC).

The mission of the deputy director is not defined precisely enough and the respective managerial attributions of the director and the deputy director should be clarified. The steering committee (PI board) should have clearer executive functions.

Although most of the scientific programs are well thought out and internationally competitive, some projects need to better exploit the unique environment of the Institut Curie to develop more ambitious and cutting-edge goals.

Recommendations

The expert committee members were favorably impressed by the scientific achievements of the groups composing the unit, by the obvious synergies and the level of collaborations between the teams, by the multidisciplinary aspect of the programs that rests on well-defined objectives. The experts committee supports the strategy that has been decided by the director, the deputy director and the group leaders. Yet, the experts committee encourages the teams to harness the incomparable scientific and medical environment of the Institut Curie to launch those inspiring projects that will integrate the main thematic axes of the unit. Following this line of reasoning, it is expected that ETIC teams participate more actively in the SIRIC of the Institut Curie on the Paris intra muros campus. This scientific ambition should be backed by the explicit will of the group leaders to obtain international sources of fundings and by taking additional leadership in international networks to reinforce the visibility of the unit. In addition, a clearer governance of the unit should be implemented with a steering committee that collectively decides the scientific issues concerning the unit. Furthermore, a more rationalized allocation of human and space resources, especially of the technical support, should become the priority to be planned by the directorial management of the unit. Of course, the success of this policy depends on the vision that the upper management at the Institut Curie has for the Orsay site. The new director of the Curie Cancer Research Center asked an ad hoc committee that met last September to make recommendations on both the structuration of the Orsay site and the governance of this campus in order to define a coherent and integrated strategy. It is anticipated that the ETIC teams will endorse the organisational decisions that are priorities in the agenda of the new direction and that they will decisively contribute to the quality of the biomedical research developed on the Orsay site.

3 • Detailed assessments

Assessment of scientific quality and outputs

Between January 2010 and June 2013, ETIC teams published 104 articles in peer-reviewed journals (this figure is the total number of articles in which the ETIC investigators are the main contributors as well as collaborative papers). The production has been steady over the past 3 years and 13 articles have been published in journals with an impact factor above 10. The average number of citations per article is around 7. The five key papers that have been selected to attest to the scientific achievement of the unit were published in PNAS, Cell Reports, J Natl Cancer Inst, Pigment Cell Melanoma Res, Clin Canc Res. Six patents have been filed by ETIC teams during this 3-year period. Collectively, these bibliometric indicators provide evidence that ETIC teams are performing well, although there is a certain level of heterogeneity among the teams in terms of scientific output.

Assessment of the unit's academic reputation and appeal

Two MCU have been recruited since 2010 and several staff scientists have been promoted (1 CR1 to DR2, 3 DR2 to DR1 and 2 PR2 to PR1). Heads of the groups and staff members are regularly invited to give communications at national/international conferences and they are actively participating in national and international networks. They are also involved in the organisation of meetings (e.g, European Melanoma Workshop, 2013; 14e International Meeting on Xenopus, 2012). Several staff members participate to scientific committees of both national institutes (CNRS, INSERM) and charities and assume high responsibilities at the Institut des Sciences Biologiques (INSB, CNRS) and at AVIESAN. Last, but not least, a new ATIP/AVENIR that is located on the Orsay site in a close-by laboratory is going to join ETIC for the forthcoming contract. All these elements attest of the unit's attractiveness. Yet in 2013, 7 post-docs developing their research in 3 of the 6 teams of the laboratory. This relative underrepresentation of post-docs indicate that the unit's appeal deserves to be increased. Accordingly, no CR permanent staff scientists have been recruited at CNRS or INSERM in the unit since 2010, indicating that the attractiveness of the laboratory for successful post-docs with strong track-records is not optimal. In consideration of these elements, it is doubtless that the unit has acquired a solid academic reputation. However, taking into account the international renown of some of the teams, it also appears that the group leaders have not capitalized on their assets to promote the unit's visibility and this is a challenge that shoud be met in the perspective of the future 5-year contract.

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

The unit's interaction with the economic environment is adequate considering the size of ETIC with 6 patents that have been filled since 2010. However, considering the original results obtained on the mechanisms of cell transformation with the identification of putative therapeutic targets, not to mention the inventive tools and models that have been developed in the unit, it occurred to the expert committee members that there is opportunity to place more priority on this branch of activity.

Some teams are committed to the translation of their research to the clinics such as team 1 which has developed innovative double stranded oligonucleotides (D-baits) to sensitize cancer cells to chemotherapy and radiotherapy. Team 1 leader founded in 2006 the startup "DNA therapeutics" and she has maintained close interactions with this biotech. Partnerships between ETIC teams and the private sector (Chanel, Sanofi) have been set up. Finally, scientists working at ETIC occasionnaly participate to large public conferences and are interviewed in TV broadcasts.

Assessment of the unit's organisation and life

The unit has two organizational bodies: a PI board and a Laboratory Scientific Council. The first instance includes the director, the deputy director and the group leaders. The operational tasks of this steering committee concern the strategic decisions on the organization of the laboratory and all issues regarding the scientific life in ETIC. The PI board meets occasionally when relevant questions have to be discussed. The laboratory council is chaired by the director and includes the group leaders, the health and safety representatives, and the administrative assistant as well as the elected representatives of staff scientists, ITA/BIATSS, post-docs/PhD students. This statutory body meets two to three times a year and has a consultative role on subjects related to the practical organization of ETIC as well

as on health and safety procedures. A report about the different questions discussed during the Laboratory Council is made available to each unit member. A general assembly of the ETIC personnel that should meet once a year is mentionned in the "rules and regulations of the unit" but is not referenced in the section of the report dealing with the organization of the unit. Finally, weekly scientific meetings are organized during which Master 2 and PhD students, post-docs and researchers present their work in front of the whole unit personnel.

During the on-site encounter with staff scientists, ITA/BIATSS and post-doc/students, the expert committee members felt that the conditions of work with respect to the unit's organization were globally positive. However, there was a general agreement among the personnel that important decisions directly impacting on the functioning of the unit and consequently on the organization of the work were not adequately shared between the PI board and the members of the unit, an aspect that should be improved.

Overall, the management and the scientifc animation at ETIC are based on relativey explicit rules and are appropriate for the functioning of a unit of this size. However, the missions of the steering committee are not explicit enough since they are not described in the "rules and regulations of the unit". This point should be corrected since the PI board meets on a regular basis and should take part in real decision-making as well as executive functions.

Assessment of the unit's involvement in training through research

ETIC teams are affiliated to Life Sciences and Health Doctoral Schools that depend on Universités Paris-Sud, Paris-Diderot, Paris-Descartes and École Pratique des Hautes Études (ED n°157, 273, 418, 426, 472). 26 PhD students have been working at ETIC since 2010 and among them, 12 successfully defended their thesis, publishing on average 3 articles during their PhD. Furthermore, 21 students in M2, 9 in M1, 16 in L3 and 2 in L2 have been trained in the unit since 2010. 11 scientists working in the unit have obtained their HDR. Overall, these indicators attest to the very good quality of tutoring at ETIC.

ETIC staff scientists including permanent staff CR/DR and of course Maitres de Conférences (MCU) and professors (PR) are involved in teaching duties at different levels of the university cursus from L1 to M2 and CAPES and even in the frame of continuing professional development for physicians. International courses have been organized by team leaders of the unit: a course in oncology (French-Chinese), Wuan, China in october 2013 and an international course entitled "From pigment cells to melanomas" in association with the Université Paris-Sud and the Institut Curie. In conclusion, the unit's involvement in training through research is largely satisfactory.

Assessment of the strategy and the five-year plan

In the perspective of the 5-year contract, the ETIC direction intends to carry on the programs that constitute the core expertise of the unit and which integrate basic studies on the mechanisms of neuroepithelium development with the exploration of how disruption of these biological processes contribue to the formation and invasiveness of neoplasia. This objective is well-founded and the unit has the scientific skills, the team leaders expertise, the access to well equiped platforms and is ideally located at the Institut Curie to succeed in its endeavour and to make outstanding contributions. As underscored in the project unit and in this report, to be effective this prospective plan requires the precise definitions of short-term and long-term objectives that include :

1) a fair division of technical support among ETIC teams;

2) allocation of more lab space to ETIC;

3) the access to bioinformatic support and to computing power, a pressing need for laboratories in the biomedical field;

4) the recruitment of more junior group leaders developing a research program that fits with the main research themes of the unit;

5) a reflection on the future managerial group since the incumbent director will not be eligible for a third mandate.

Some of these goals strictly depend on the strategy that will be implemented by the direction and by the group leaders of ETIC. Others (items 2 and 3) are in the purview of the scientific direction of the Institut Curie since they rely on a policy that reassigns or apportions lab space on the Orsay site and on the decision to develop a bioinformatic

group on the Orsay site (in coordination with the Paris site), a proposition recommended by the ad hoc committee and that would definitely boost the research of biomedical units on the Orsay campus.

4 • Team-by-team analysis

Team 1: Recombination, repair and cancer : from bench to bed

Name of team leader: Ms Marie DUTREIX

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	1	2
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1
N6: Other contractual staff (without research duties)	5	5
TOTAL N1 to N6	**8**	**9**

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

• Detailed assessments

Assessment of scientific quality and outputs

Team 1 develops translational research in cancer chemotherapy although maintaining activity in the scientific field of DNA repair activity. The choice of the group was to target DNA repair activities in order to sensitize cancer

cells under a co-treatment protocol with radiotherapy or chemotherapy with clastogen agents. The team leader chose to counteract the initial step of recognition of DNA breaks ends by delivering short double stranded oligonucleotides (D-baits) in cells. Dbaits activate both DNAPK and PARP activities. More recently, the team tested Pbaits that mimic single-stranded DNA, an activator of PARP. Indeed, the mechanisms of cell sensitization to radiotherapy or chemotherapy rest on an indirect effect rather than a direct competition reaction with Ku70/Ku80. Nevertheless, Dbaits have been tested in mice showing an effect on the reduction of xenograft growth and are under clinical phase 1 trial.

This research area, inhibition of activities of DNA double-strand break repair, has been a subject of investigation for the last 15 years. Various inhibitors have been selected but the limitation in their therapeutic development was due to the low specificity of most of them as kinase inhibitors and to the fact that these agents should be used in combination with radio or chemotherapy. However, a toxic effect of PARP inhibitors was shown in cells deficient in the homologous recombination (BRAC1-BRAC2 tumors)(Bryant et al, Nature 2005). Such results have boosted the research for DNA repair inhibitors which is also reinforced by the recent determination of the structures of ligases (specially lig3 and lig4), artemis and cernunnos complexes.

In parallel, team 1 identified new targets phosphorylated by DNA-PK with an interesting result on the potential involvement of this PI3KK in cell migration.

The findings are reported in 16 original articles (9 as last author), 1 review, 1 news and views, 5 patents with extensions in 2011 and 2012 for the last two ones and issued in several countries for 3 of them. The reviews belong to the DNA research area with 2 Nucleic Acids Res in 2013, the medical area with Clin Cancer Res (2009), J Gastroenterol (2012) as well as the biological area with JBC (2012), PNAS 2012 (one page related to the JBC paper) and 2 PLoS ONE (2012, 2009). This illustrates the capacity of the team to publish the results in highly ranked journals.

Taking into account the 60% time in academic work declared in the activity profile of the team, the number and quality of the articles as well as the 5 patents, it can be concluded that the team output is of a high level. In adition, this parameter should be taken into consideration, the team leader is the only one researcher with a permanent position in the team.

Assessment of the team's academic reputation and appeal

Different points illustrate the reputation of the team:

Team 1's PI obtained different grants with a mean of about 200 k€/year (in 2013, 193 k€ for the RADEX plateform could be deduced from the total amount of 346 k€). Among the grants, one can mention a partnership in the European STREPP "Bioemergence" program and 2 ANR. The team leader coordinates the 3rd ANR grant.

She was invited as a speaker at 12 international meetings and six national meetings.

In the Curie Institute the PI coordinates the PIC (Programme Incitatif et Collaboratif, Institut Curie) BioSystems 2013-2017, comprising 10 teams as well as the axe V (radiobiology and radiotherapy) of SIRIC-Institut Curie. The PI received 2 prices and was awarded the national honor "Chevalier de l'Ordre National du Mérite" in 2013. She participates in the reviewing procedure of manuscripts.

The PI is fully recognized by various scientific and academic institutions in the specific field of siDNA in therapy both in academic and in industrial institutions.

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

The most prominent participation of team 1 in this area corresponds to the links it makes between academic research and industry. The involvement in translational research is outstanding. The team leader is co-founder of the startup DNA Therapeutics (2006) and received ongoing support from this company (technician, research funding). She is still member of the advisory board and serves as a consultant acting as chief scientific officer (CSO) to lead the company reaching clinical phase 1.

She received several awards for the creation of the start-up company (Oseo, Senat, Biovision, etc.).

The team belongs to a Carnot Institute. In line with the collaboration with a start-up working in human drug therapeutics, the team follows ISO procedures.

The participation of the PI in communication media is shown in a cartoon explaining how Dbaits works (www.youtube.com/watch?v=95Tf4wFsK7Q) and by different debates and interviews (Journal de la Recherche, Biofutur, France 5, Santé magazine, France Info, France Culture, France Inter, 2012, etc.).

Assessment of the team's organisation and life

The team is composed of a single senior scientist. The team leader participates in the council committee of the unit.

Assessment of the team's involvement in training through research

The team leader was involved in student mentoring (2 PhD students defended their thesis in 2010 and 2013) and 2 Master-2 students. She gave teaching courses at the level of Master degree and PhD on DNA repair. Thus, her participation in the training corresponds to what could be expected for a research director.

Assessment of the strategy and the five-year plan

The stabilisation of the group was taken into account with the recruitment of a CR1 CNRS who is a specialist in DNA repair and radiation damage. In addition, a radiotherapy oncologist (MD,PhD) will collaborate with the team for 10% of her time.

The proposed projects are in the continuation of the programs developed during the former contract, however with stronger emphasis on radiobiology corresponding to the expertise of the newly recruited CNRS researcher. The project on the overexpression of DNA-PK in skin and uveal melanoma metastasis should provide new insigths into the role of DNA-PK outside the cell nucleus.

Owing to the strong links with DNA Therapeutics, the phase I trail with DT01 and other D- or PBaits in combination with radiotherapy to treat local melanoma metastasis will continue. However, it is consistent that DNA Therapeutics collaborates with international pharmaceutical companies to be able to reach a market.

Conclusion

- **Strengths and opportunities:**

The team leader has developed expertise in radiobiology and experimental radiotherapy; this area will be reinforced by the recruitment of a PI working in radiotherapy. The translational research is outstanding since the transfer from bench to bedside has been really made.

- **Weaknesses and threats:**

It is anticipated that it will be difficult to maintain both translational and academic research programs in the case of a small team. However, so far, this challenge has been successfully met with a good ratio of publication/number of PhD.

The DNA-PK research area is very competitive and the role of this PI3KK protein other than in DNA repair should be approached in collaboration with PI(s)familiar with metastatic development, in or outside the unit.

- **Recommendations:**

In addition to the CNRS researcher who will join the team and because the present team leader will retire in 2020, it is important to recruit another PI in order to stabilize the group. Therefore, additional space lab is necessary.

Because the academic research is devoted to radiobiology and DNA repair, the melanoma model might not be the most appropriate for radiotherapy projects although it might be interesting in the field of the modulation of DNA repair activity as well as new roles of DNAPK. Consequently, due to the recruitment of the CNRS researcher, a radiobiologist, the team should, if possible, collaborate internally with the team of a newly recruited junior scientist and/or team 2 working on medullablastomas, a pediatric tumor treatable by radiotherapy.

Team 2: RAF and MAF signaling in oncogenesis and development

Name of team leader: Mr Alain EYCHÈNE and Mr Celio POUPONNOT

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

Team 2 has two major research themes focused on two oncoprotein families, e.g. RAF (ARAF, BRAF, cRAF) serine/threonine kinases working in the RAS/RAF/ERK cascade (one PI primarily involved). The second topic deals with the AP-1 MAF (MAFA, MAFB, cMAF) superfamily of transcription factors (both PIs involved), and on the role of protein phosphorylation in modulating biological responses that are relevant to development and oncogenesis. The RAF project stems from the identification of a retroviral counterpart (EMBO J, 1988) and led to major discoveries such as the role of BRAF in melanocyte stem cells (Cell Rep, 2012), as well as the regulation of the pathway by KSR (Curr Biol,

1998). The MAF project stems from the identification of one of its transcriptional targets, namely the QR1 retina-specific gene (Mol Cell Biol, 1995) and also led to major contributions such as the role of GSK3-mediated phosphorylation in regulating its activity (Mol Cell, 2007) and a role for MAF in DRG sensory neurons (Dev Neurobiol, 2010).

New concepts have been developed by the team, including:

I) the role of splicing in BRAF effects in cancer and development;

II) the role of the RAF family in melanocyte development and stemness (melanocyte stem cells, MSC);

III) the contribution of phosphorylation in MAF regulation (a pathway amenable to therapeutic intervention);

IV) lineage-specific roles of MAF as an oncogene/tumor suppressor.

Overall, the scientific output of the team is excellent includes 16 peer-reviewed articles in the 2008-2014 period. It is focused on the 2 major research themes and it is well-ranked: the two team leaders' full track-records feature 58 papers and 28 papers respectively. The most compelling publications include one Mol Cell 2007 paper on MAF (both team leaders co-corresponding authors), one Cell Rep 2012 paper on RAF (AE last author), and one Nature Cancer Rev 2008 on MAF (the two team leaders as first and last authors). Some of these discoveries were acknowledged by journal issue covers (Nature Cancer Rev and Dev Biol).

Assessment of the team's academic reputation and appeal

Both PIs participated to several advisory boards and steering committees, mainly of national French Institutions. Currently, the team is well-funded (one Ligue Nationale Contre le Cancer labelisation grant and one INCa contract are ongoing up to 2017 and 2016, respectively). The team has been successful in getting financial support in the past years from French agencies (Ligue Nationale Contre le Cancer, ARC, INCa).

One PI has been nominated Scientific Deputy Director of CNRS (INSB) and Deputy Director of ITMO Cancer (AVIESAN).

Post-doc and students turnover is fine; some post-docs/students were from abroad (Australia, Tunisia).

The good reputation of the team is attested to by the fact that both PIs have been invited to 16 conferences; one the two PIs was invited speaker at 7 international meetings. The reputation is also shown by the good number of national and international collaborations, including those with leaders in the field of BRAF.

The two PIs have been reviewers for top international journals; one, in particular, has contributed as a reviewer for French and International agencies, including ERC, AICR, Cancer Research United Kingdom.

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

Besides scientific publications, dissemination was supported by a number of TV and video interviews and press releases.

Assessment of the team's organisation and life

The overall team organization is sound with two major interconnected themes and two PIs having prime responsibility for each one. In the future, the new responsabilities awarded to the first PI, make it reasonable that the second one is going to co-lead the entire team and not only the MAF project. This will also guarantee increased recognition of the co-PI. At the beginning of the contract, the team included 10 members including 1 DR1, 2 CR1, and 1 IE1. One post-doctoral fellow and 1 PhD student completed their program during the contract and 1 Engineer, 2 PhD students and 4 students were recruited.

Unit infrastructures and intra-unit collaborations are considered to be good premises for research activity of the team.

Assessment of the team's involvement in training through research

Both PIs are involved in teaching activities. Students turnover, with 5 new students recruited and one who defended his thesis during the contract, attests of a sound guidance.

Assessment of the strategy and the five-year plan

The RAF field is highly competitive; still the team has selected original questions to explore, (e.g. the role in normal development), that are grounded onto a solid basis (Cell Rep 2012 paper). The MAF project is very novel, in particular regarding MAF's role in neoplasms (including the role of NRL-MAF in group 3 medulloblastoma) and development (as suggested by the striking phenotype of mice expressing a non-phosphorylatable MAF allele).

The RAF program is in line with the team recent discovery of BRAF role in melanocyte stem cells (MSCs), and envisages an extensive use of mouse models generated to address features of MSCs and the role of BRAF in NRAS-mediated melanomagenesis. The MAF program focuses on the tissue-specific oncogenic role of MAF, and is based on an extensive use of transcriptomics, orthotopic models and neurosphere assays, and the new observation that the NRL-MAF is selectively upregulated in medullobastoma.

The strategy is sound and homogeneous across the different themes, involving the extensive use and construction of conditional mouse models. The credibility is supported by the fact that this new approach already yielded results with conditional RAF and MAF knockouts.

Initially, the team's contributions have been mainly based on biochemical and in vitro based cell studies. More recently, the team has correctly switched to animal models. This has been achieved with a good strategy based on acquisition of mouse handling expertise by two senior scientists and recruitment of an engineer.

The two PIs identified the potential weakness of a thematic dispersal through their diversity of fields (cancer, neurobiology), and they correctly reframed their strategy to a more cancer-focused approach; the threat of having a relatively small laboratory is mentioned but apparently this will not be an obstacle to the development of these projects.

The plan is felt to be feasible based on the team expertise, secured funding and available models and collaborations.

Conclusion

- **Strengths and opportunities:**

The team has a historical and international recognition in the field, and is developing research based on original animal models that is innovative, especially on the role of BRAF in stemness and MAF in tumor development.

- **Weaknesses and threats:**

The potential weaknesses of the overcommitment of the group leader has been solved by proposing the transition to a more frontline role of the Deputy director who will co-lead the team.

- **Recommendations:**

Carefully plan the coordination of the two projects focused on BRAF and MAF which implies to thoroughly defining the questions addressed and deciding the allocation of human and funding resources according to the perceived potential of each topic during the forthcoming 5-year contract. Try to recruit post-docs.

Team 3: Normal and Pathological Development of Melanocytes (NPDM)

Name of team leader: Mr Lionel LARUE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)	1	
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	2
N6: Other contractual staff (without research duties)	2	2
TOTAL N1 to N6	**10**	**8**

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

• Detailed assessments

Assessment of scientific quality and outputs

Team 3 has continued to produce and publish original research of a high standard, in the field of melanocyte/melanoblast development and melanoma. They have a special focus on β-catenin (bcat), its signalling pathways and interactions, and also specialize in the production and study of transgenic mice for analysis of gene functions. The team has published 39 original articles, 19 reviews/chapters and 2 patents in the assessed period 1/2008-6/2013, on widely ranging topics and often in excellent or very good journals. There are 11 last-author papers in JCI, Development, PCMR [JIF 5.8], MCB, etc., and 28 collaborative papers in Cell, Nature Medicine, Cancer Cell,

JNCI, etc.) with an overall average JIF=6.1. Among key published advances have been the demonstration that bcat promotes melanoma metastasis yet retards local cell migration; the identification of a proliferative role in normal development for BRN2 (oncogenic in melanoma), and the collaborative identification of MDM4 as a factor that commonly blocks p53 signalling in melanoma and provides a new therapeutic target.

The team's work is widely cited (PI, 670 citations in 2012), and their international reputation is evidenced by numerous invitations to speak at international conferences (including some broader conferences, e.g. cancer, bioengineering), and at major overseas institutions, their collaborations with groups in other countries e.g. the USA, United Kingdom, Switzerland, Italy and their participation in international committees (next section).

Assessment of the team's academic reputation and appeal

The PI and other team members have been involved in a wide range of international and national projects. Among leading roles, the team leader has been President of the European Society for Pigment Cell Research, president of the steering committee of the French PAIR (Programme d'Actions Intégrées de Recherche) on melanoma (from INCa, ARC and the Ligue Nationale Contre le Cancer/LNCC) and co-ordinator of an INCa "Projets Libres en Biologie" or PLBIO. He was vice-president of the large IPCC conference (2011), and co-organizer of about 10 other conferences. He has been a member of numerous other scientific networks and societies, international and national committees including INSERM's scientific committee CCS6 (2008-2012), and 5 editorial boards. He has reviewed for leading international journals (e.g. Science, Genes & Development) and overseas research sponsors (e.g. Wellcome Trust, FSO Flanders). He has several awards from INSERM. Another team member has also received several international conference invitations and one prize (from LNCC); she has been president and member of ARC's CN3 committee, and has participated in organizing conferences. Other team members have also had conference invitations and reviewed manuscripts.

Attractiveness for recruitment: the team has recruited postdoctoral and doctoral researchers from 7 other countries in this period, and several of these (especially where recruited in earlier years) have co-authored several high-quality papers subsequently. This suggests a good level of attractiveness of the team, although there is no mention that any post-doctoral fellow from the team has competed for a permanent position at CNRS or INSERM in this period.

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

More than 80 MTAs were signed for sharing mouse strains around the world. Several methodological papers were published in the period with last authors from the team, e.g.: Efficient gene expression profiling of laser-microdissected melanoma metastases; general strategy to analyse coat colour phenotypes in mice; automated cell tracking and analysis in phase-contrast videos. Two pieces of online software were published. All these are valuable to researchers in the specialized fields.

The team reports a 3-year industrial partnership with Chanel (1/2011-12/2013), producing 2 joint patents regarding uses of microRNAs in modification of pigmentation (no publications mentioned).

The PI has been a member of two animal research ethics committees (president of one), in addition to various scientific networking roles and editorships mentioned above.

Interactions with the wider community include participation in large public meetings to talk about cancer and vitiligo (the team leader), certain web sites (not detailed), and a number of press releases on their research.

Assessment of the team's organisation and life

Brief comments: it is clear that the unit's animal facility is crucial to team 3, and is presumably shared with other teams. There are signs that this team seems to be considerate regarding the career-development needs of its younger researchers, who have attended and presented at conferences, gained teaching experience, and could publish their work in a timely way.

Assessment of the team's involvement in training through research

The team reports that 14 students completed various stages of research training in the reporting period,

including 4 PhDs completed since 2010. Four other PhD students continue to work in the group, also two masters students and one L2 (Undergraduate year 2). Overall, this is a quite good activity. The data do not indicate any problems with research-student guidance, though there is no information on subsequent postdoctoral employment.

Team members have also taken part extensively in taught courses (~550 hours total). The team 3 PI has been a co-organizer of an international (European) course for Université Paris Descartes, and a Chinese-French course in Wuhan, China. Team members have also taken part in numerous PhD and HDR examinations including 8 overseas PhDs.

Overall the team seems to be contributing well to research (and other) training, and assessment.

Assessment of the strategy and the five-year plan

The proposed research continues from the team's past and present work, taking advantage of their expertise in creating transgenic mice and their existing mouse resources, while also using cultured cell lines and an existing bank of human melanoma samples. They propose to move more in the direction of inducible rather than fixed genetic changes in the mice, to investigate the role of genetic changes at certain times. A novel direction is to target the inducible expression/deletion to include hair-follicle melanocyte stem cells (MSC), by using the promoter of Dct, expressed in MSC (as well as melanocytes and melanoblasts). The resulting mice would contribute to studies of both melanocyte development/maintenance and melanoma. The group's central interest in the bcat pathway in melanoma initiation will be extended by a study of a number of bcat-interacting factors or apparent targets (BRAF/NRAS, NF1, CAV1, ICAT, etc.) with specific approaches to vary according to existing knowledge, but with novel elements including microRNA and ChIP analyses in different cases. The BRAF/NRAS interaction study seems especially interesting. There are also genetic studies of melanocyte development and maintenance and investigation of a possible novel signalling pathway from ultraviolet light. One query on a minor point of strategy: in part 1a2, surely to model giant naevi at birth, one should induce the oncogene well before birth, not after birth.

The work seems to form an integrated package, and to comprise an appropriate combination of more straightforward and "safe"/feasible research with more novel and higher-risk investigations. In the novel class seems to be their Aim 3, of analyzing apparent signalling from UV light through bcat to DICER (enzyme involved in generating miRNAs).

The plan comprises basic rather than applied research, but findings may be clinically applicable in the future, to therapy, diagnosis or prevention of melanoma and perhaps of some other pigmentary disorders.

Non-academic partners: interactions with industry and a start-up company are mentioned in the SWOT analysis, although not specifically in the proposal.

The SWOT analysis is helpful, and generally positive. Noted threats are the possibility of a sudden rise in animal costs, and the loss of a technician; if not replaced, this will reduce the efficiency of the pre- and post-doctoral researchers.

Conclusion

- **Strengths and opportunities:**

The team has a strong reputation, many international and national links and collaborators, and a good critical mass to maintain its expertise in transgenesis and other approaches. It has a valuable resource of mouse melanoma models. Some links with industry are reported. It is currently well funded, despite the current economic situation.

- **Weaknesses and threats:**

The team reports the loss of a technician from 12/2013, and issues with office space. Because the establishment of mouse models is slow, any lapse in funding could endanger projects in progress. All three directors of research are relatively senior, an issue for the future of the team although not in the forthcoming period.

- **Recommendations:**

Support for replacement of the technician who left.

Team 4: TGFß and Oncogenesis

Name of team leader: Mr Alain MAUVIEL

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)	2	2
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	2
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**5**	**6**

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

• Detailed assessments

Assessment of scientific quality and outputs

The team has been focusing mainly on TGFß signalling in melanoma. The team has a strong international recognition in the field of TGFß. In 1998, the PI described the COL7A1 gene as the first endogenous target gene of the canonical SMAD pathway of the TGFß signaling, a major breakthrough. The PI is considered to be the French leader in the field of TGFß signalling, a pathway that is deregulated in virtually all cancers. Among major advances of the team during the last five years, they identified the transcription factor Gli2 as a direct target of TGFß/SMAD signaling, independent of the Hedgehog (Hh) pathway and established that it regulates critical events during melanoma

progression. The team has also decrypted certain mechanisms regarding the relationship between TGFß signalling and M-MITF, Ski/SnoN and the EMT switch. The team has demonstrated in preclinical models, that targeting TGFß signalling in melanoma could impact bone remodelling occurring during metastasis providing support for TGFß-based therapeutic strategies and that halofuginone could impede melanoma brain and bone metastases. Very recently, the team has profiled the Hippo pathway components in melanoma and identified the Hippo effectors YAP and TAZ as promoters of melanoma invasion and metastasis. An obvious strength of the team is its capacity to decipher intricate signalling pathways, such as TGFß-Smad, Hh and Hippo, to identify their relevance of these interactions in cancer (especially melanoma), and to create a continuum between basic research and potential clinical application. The excellent quality of this research is illustrated by:

1) a proficient production of articles where team members are in first and/or last position published in excellent peer-reviewed journals. Indeed, since January 2009, the team published 9 original peer-reviewed articles (JNCI, Cancer Res, Pharma Therap, JID, PCMR, Mol Cancer) and more than 10 comprehensive reviews/book chapters (Oncogene, FEBS Letters, JID, PCMR). Note that PCMR and JID are considered among the best journals in the specialty of dermatology. It is important to emphasize that such a proficient production is outstanding for a small group (6 people). 2 out the 5 “key” publications involving more than one team from the unit claimed by the unit are authored by the team leader;

2) numerous invitations (13 since 2010) to prestigious international meetings in both the fields of TGFß and dermatology (including 3 FASEB conferences);

3) excellent bibliometric indicators (H factor, citation rate);

4) fruitful collaborations (more than 10 original articles and/or reviews published in Cancer Res, JBC, etc.), some of them with world leaders in the field of TGFß attesting once again to the international recognition of the PI, the dynamism of the team and its capacity to collaborate.

Assessment of the team's academic reputation and appeal

The team 4 PI is a former member of the CSS7 INSERM study section (Epithelial Systems). He is an adjunct associate professor in the department of Dermatology and Cutaneous Biology, Jefferson Medical College (Philadelphia, PA, USA). The team is well endowed: the PI is a coordinator of a PAIR (Programme d'Actions Intégrées de Recherche) melanoma network (INCa/ARC/Ligue Nationale Contre le Cancer) and has a recurrent and secured grant from the Ligue Contre le Cancer (Equipe Labellisée 2011-2015). He is also a reviewer for leading and recognized international journals (Nature Genet, JCI, JNCI, Circ Res, Cancer Res, Oncogene), and French (Ligue Nationale Contre le Cancer, ARC) and foreign (National Science Foundation, Arthritis Research Campaign, Austrian Research Fund, Flanders Research Fund) research grants. He is an honorary member of the Korean Society for Investigative Dermatology, he is a former member of the European Society for Dermatological Research and he is currently a member of 3 editorial boards (JID, JDS and PCMR). The team has recruited one postdoctoral fellow from India.

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

The team has a research contract with SANOFI (2013) regarding the role of TGFß in fibrosis and wound repair. Interactions with the wider community include a number of press releases on their research.

Assessment of the team's involvement in training through research

The team reports that 7 students completed various stages of research training in the period under review, including 2 PhDs who defended their thesis. One PhD student is currently working in the team. The team leader participated in several PhD and HDR committees. He is a member of the organizing committee of the First Chinese-French Course on Oncology, Wuhan, China, October 21-25, 2013.

Assessment of the strategy and the five-year plan

The proposed research project extends the current work of the team and consists in a mix of basic and applied and translational studies, with findings that could be clinically relevant to therapy or diagnosis of melanoma and other cancers. The project is ambitious, and of extremely high quality, addressing pertinent questions in the field of

oncology, especially in melanoma and medulloblastoma. The general aim of deciphering the biochemical interaction between:

I) TGFß signaling and Hh signalling;

II) TGFß signalling and Hippo signalling, is very innovative, placing the team at the forefront of innovations in this field. The proposed work could lead to ground-breaking discoveries in the field of cancer treatments regarding the importance of the TGFß, Hh and Hippo pathways (combination of inhibitors targeting these pathways).

This integrative view and the transversal design of the proposal should be acknowledged. The PI has demonstrated in the past that he has the required experience to complete such an ambitious research program. Indeed, the small size of the team that could be perceived as a potential weakness, is overcome by the very large network of collaborators around the world (attested by many collaborative publications) as well as the capacity of the PI for adaptation. The long and successful experience of the PI as a group leader should guarantee that the team makes the best strategic choices regarding the results obtained in the different research axes that will be developed over the next five years, granted the feasibility of the five-year plan. Moving towards mouse model approaches in close interaction with team 3 is a good move. The project is well balanced regarding the "secured" and more "risk-taking" specific aims (possible due to the presence of two technical members of staff with permanent positions). It is acknowledged in the SWOT analysis that both lab and office space limitation is a constraint for this team, as for the others in the unit, that undoubtedly limits the growth of the research team.

Conclusion

- **Strengths and opportunities:**

The project is relevant, ambitious, innovative and transversal.

International recognition of the team and PI.

Many local, national and international collaborations.

The team is well funded.

Two technical staff with secured positions granting the continuity of the long-term projects.

- **Weaknesses and threats:**

Lack of critical mass resulting from the small size of the group, which cannot increase in size because of space constraints.

As mentioned by the PI, it is important to give priorities to the different mouse projects regarding:

1) the space allocated for their mice in the animal facility;

2) the funding;

3) the number of people working in the lab.

- **Recommendations:**

To be supported by the unit in terms of providing an optimal working environment.

Recruit a clinician.

A permanent staff CR researcher from the team should get more visibility in the future (participation to international meetings, grant applications).

Considering the international expertise of the PI, a greater implication in steering committees/study sections should be considered.

Team 5 : Signaling and neural crest development

Name of team leader: Ms Anne-Hélène MONSORO-BURQ

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	3
N2: Permanent EPST or EPIC researchers and similar positions		1
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**5**	**6**

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

• Detailed assessments

Assessment of scientific quality and outputs

The PI has made important contributions to understanding the genetic network activated over time during the differentiation of an embryonic mesenchymal cell population, the neural crest (NC). Her team has detailed the critical roles of certain highly conserved transcription factors among vertebrates, which all have a role in NC development. Reactivation of parts of this pathway in other spatial and temporal contexts is heavily implicated in cancer and metastasis, and the group has identified key transcription factors that are activated in response to signalling cues and instrumental in conferring cellular identity and behaviour. Over 2008-2013, the group has produced 11 original papers (10 in senior positions), of which 2 recently appeared in a competitive general science journal (PNAS). Their most

recent publication (February 2014) in the specialized journal, Developmental Biology (formerly the top in the field and still esteemed), is in a back-to-back position with complementary conclusions drawn by a highly reputed senior American laboratory. Each paper cites former work of the other group, demonstrating the recognition at an international level. Given the experimental difficulty of the approaches and prestige of the journals, this is a commendable rate of scientific production.

Assessment of the team's academic reputation and appeal

The PI is the coordinator of an international Agence National de la Recherche network, CRESTNET, with 4 partners. The recent recruitment of two talented French developmental neuroscientists with permanent positions, shows how attractive this group has become within the developmental biology community and how well it gets along with its departmental colleagues. The team maintains a network of international collaborators that were seeded by the PI sabbatical in the US where she has been invited to give seminars at UC Berkeley and Caltech. The Pi has also given plenary talks in 5 meetings in France and Canada. Two prizes reflect her commitment to teaching. The journals for which she is a reviewer are all the best ones in developmental biology, and she is also a reviewer of grants for 5 international and 4 national science foundations, as well as for a large granting non-profit association.

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

The team uses both innovative tools but more often, innovative applications of modern tools in experimental developmental biology. This approach enables them to obtain valuable results in a credible manner, which is supported by the success of their publications. The PI has participated for a number of years in national committees for biology teacher recruitment and has had an officer position with French professional societies. She participates in outreach for her institution, having written for the layperson-oriented Journal of Institut Curie.

Assessment of the team's organisation and life

The scientific goals and division of labour on the team appears coherent. All members have participated in publications, which bodes well for the new members arriving. The teams in the unit appear to work in a collegial manner together and work with many common resources. The laboratory council is logically constituted and meets a minimum number of times a year, with the PI present, while the engineer in the team is Health and Safety Officer. The space allotted to the team is sorely deficient in both lab and office.

Assessment of the team's involvement in training through research

The PI had a personal award from 2005-09 for special involvement in doctoral training in addition to her normal teaching load. Following this, she has mobilized her team and beyond, with the unit director, to develop from scratch a one-month international training course (5, now 10 ETCS) for 2nd year masters and PhD students and postdoctoral fellows, on pigment cell and melanoma development. For the 3rd year in 2014, the unit director, the PI and a new member of her group are organizing and instructing this interdisciplinary course. In the PI's own group, over the past 5 years, 2 PhD and 10 masters-level students were trained (one Ph.D. taking four years, a not unusual circumstance, and a second one having started in 2011). Involvement with graduate and postgraduate training schemes through research is therefore highly committed and effective, and not spread thin.

Assessment of the strategy and the five-year plan

Four objectives are laid out. The strategy was presented as a logical and ambitious outgrowth of the initial results on the network programming EMT and multipotency characteristics of the NC population. The first objective is immediate short-term work completing a recently published article on Pax3 gene targets, by validating those remaining. The frog model is well adapted for assessing the effects of changes in expression of these genes. The team has sent its engineer for a week's training in ChIP, which they propose to do followed by deep sequencing. They will focus on effectors from earlier identified pathways, using both *Xenopus* and human iPS models and mouse models of *Pax3* alleles, available from Parisian collaborators. The second objective is to deepen the exploration of how Pax3 and Zic2, and a third transcription factor, Barhl2, regulate signaling in the specification of NC cells and dorsal brain in *Xenopus*. The reinforcement of the team with two brain researchers on this project will aid in achieving this goal. The third objective is more risky as it proposes moving into a highly original study of the role of enzymatic regulators

of metabolism in NC specification. There is a need for more research into the possibility that metabolic changes driven by these and similar genes are hallmarks of EMT, leading into the 4th objective. This is to examine the roles of the genes studied in the previous goals in their physiological context, within the pathological context of two neural crest-derived cancers (pheochromocytoma and melanoma). This work will take place with both internal and external collaborators. While the technical approaches are classical, their combinations in resolving problems of fate specification and separation of cell lineages and potential remain innovative. All these goals are realistic if ambitious, and within the reach of the team.

Conclusion

- **Strengths and opportunities**

This is an internationally recognized, competitive group with productive and excellent quality of contributions to knowledge.

An attractive mix of inter-related projects both within the team and the department promise novel and significant findings.

The PI has developed appropriate collaborations both within France and internationally.

- **Weaknesses and threats**

Financially, the group needs a new research grant for the next period.

The areas of both laboratory and office space currently allocated to this growing team as to the department as a whole are woefully insufficient and risk stunting their growth and contributions to the community.

- **Recommendations**

This group has performed very well during the period of assessment and is encouraged to continue in this top quality vein over the coming years.

The proposed projects are well structured and relevant.

Team 6 : PAX and MITF in signaling eye development and melanoma

Name of team leader: Mr Simon SAULE

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

The team has studied Uveal Melanoma (UM), a form of ocular melanoma that genetically differs from skin melanomas. During the past contract, the group has provided evidence that the tyrosine phosphatase PTP4A3 (also named PRL3) is overexpressed in a fraction of UM that are prone to metastasize. Several substrates of PTP4A3 have been identified by the group including CRMP2, a modulator of microtubule dynamics. Furthermore, PTP4A3 is a phosphatidyl inositol 4, 5 phosphate (PIP2) phosphatase. Results obtained by the group have shown that this phosphatase is physiologically involved in neural crest cell migration and promotes cell invasion in melanoma models.

The goal of the team in the forthcoming contract is to delineate how PTP4A4 controls the cytoskeleton and metalloproteases activation to foster cell migration and invasion.

The publication record of the team during the 2008-2013 period is good (11 articles, of which 7 have been contributed as a first author and 3 as last author). A MCU who has recently joined the team and had been working in another team, published in top ranking journals but in an intermediate positions (Cell 2013, JCI 2011, JEM 2011, Nat Med 2011, EMBO J 2008). The best publication of the team as a proper work was published in 2011 in Cancer Res (IF 8.6). The other publications are in journals with an IF between 4 and 7.

The team leader has active collaborations with team 4 and with teams of the Department of Translational Research, Institut Curie, Paris and these collaborations have led to publications (JNCI, 2010). The strong collaborations with the Curie Hospital and the technology transfert department are a real asset for the team.

Assessment of the team's academic reputation and appeal

The team leader is coordinator of national projects: a Project DGOS-INCa 2012-15 "Genetics of Uveal Melanoma", therapeutic target identification and preclinical validation. The team leader is coordinator of the PIC retinoblastoma (2010-13) and of the Translational Department project Uveal Melanoma.

The team is member of the labex CellTisPhybio.

The PI has been an expert for the ITMO BCDE of AVIESAN since 2010 and expert on national committees (Ligue Nationale contre le Cancer; Retina France, CCSU 64-69, etc.). He has also been invited at 5 international meetings in ophtalmologic oncology. Overall, the group leader is involved in several networks and his reputation in UM is nationally and internationally recognized. However, the attractiveness of the group for post-doc seems rather low.

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

This has included scientific expertise for the Région Centre (2012), presentation in front of Retina France patients and their relatives (2009 and 2011) and participation to the "journal des donateurs de l'Institut Curie" on the topic of retinoblastoma.

Assessment of the team's involvement in training through research

The team leader mentored 3 PhD students and one post-doc over the last 5 years period. The group leader is Professor and consequently highly involved in teaching.

In the future, with three MCU (two MCU joined the team in 2013) and one senior professor, the group should have the workforce to provide a high quality environment to mentor the students.

Assessment of the strategy and the five-year plan

The proposed project is a continuation of the program dealing with UM. It is mainly focused on the analysis of the molecular mechanisms leading to metastasis in UM through the identification of physiological substrates of PTP4A3. The proposed project follows two main axes. The first one aims at studying genes likely involved in the metastatic process such as CRMP2, the target of PTP4A43, but also PRKDC a kinase involved in non homologous end joining. The second axis will be focused on the role of two transcription factors known to be involved in the development of the neural crest (AP2α and MITF) and in melanoma (MITF). The goal here will be to understand if PTP4A3 acts upstream or downstream in signalling pathways that implicate MITF and AP2α.

One interesting internal collaboration with team 1 is mentioned to use one of the protein (PRKDC) as a new target for therapy.

Clinical collaboration and the use of interesting mouse models (fresh UM tumors xenografted in nude mice) are no longer mentioned but we were told orally that these models are maintained as part of the team's arsenal.

Conclusion

- **Strengths and opportunities:**

Recognized expertise of the team and of the group leader in the research on UM.

The choice to focus the research on UM is strategically sound considering the recognized clinical activity of the Institut Curie in the treatment of UM.

Participation in several networks including the Labex CelTisPhyBio which should boost the research of the team.

- **Weaknesses and threats:**

The project is solid and in direct line with the previous one, but is not cutting-edge and too focused on the mechanistic dissection of PTP4A3 targets. Furthermore, this program shies away from in vivo models that are required to firmly establish the in cellulo data. The risk-taking of the proposed project is low, yet the group is ideally positioned to develop new projects on UM and to strengthen internal collaborations with groups working on melanoma or neural crest.

The absence of post-docs needs to be corrected, particularly in view of the high level of funding obtained and the number of senior positions in the future team.

The scientific production is average.

- **Recommendations:**

The study of UM is opportune and the group is well positioned at the Institut Curie to develop this program. This line of investigation should be actively pursued but a balance between a solid research, as developed by the group, and more ambitious projects should be found.

The translation aspect of the research program could be strengthened given the collaborations with the translational department of the Institut Curie.

The recruitment of scientists with permanent positions and of post-docs would reinforce the team and open opportunities to launch more ambitious projects.

5 • Conduct of the visit

Visit dates:

Start:	Thursday 20th February 2014 at 09:15 am
End:	Friday 21th February 2014 at 04:15 pm
Visit site:	Centre de Recherche d'Orsay
Institution:	Institut Curie
Address:	Bâtiment 111, 91405 Orsay
Specific premises visited:	Visit of the laboratory

Conduct or programme of visit:

Thursday 20th February 2014

09:15 am	Welcome to the experts committee
09:30-10:00 am	Preliminary meeting of the experts committee (closed hearing) *Attending: expert committee members and AERES Scientific Delegate (DS)*
10:00-10:10 am	Presentation of AERES evaluation and of expert committee members
10:10-11:00 am	Presentation of the research unit by the director (including questions) *Attending: expert committee members, DS, representative of institutions and unit members*
11:00-11:45 am	Meeting with representative of Institutions *Attending: expert committee members, DS, representative of CNRS, INSERM, Paris 11 and Institut Curie*
11:45-01:00 pm	Lunch
01:00-02:00 pm	Scientific presentation team 1 *Attending: expert committee members, DS, director of unit, representatives of institutions and unit members*
02:00-02:30 pm	Scientific presentation newly recruited team
02:30-03:30 pm	Scientific presentation team 2
03:30-03:45 pm	*Break*
03:45-04:45 pm	Scientific presentation team 3
04:45-05:45 pm	Scientific presentation team 4

Friday 21th February 2014

08:45-09:00 am	Closed door experts committee meeting
09:00-10:00 am	Scientific presentation team 5
10:00-11:00 am	Scientific presentation team 6

11:00-11:15 am	Break
11:15-11:45 am	Meeting of the experts committee with technical and administrative personnel
11:45-12:00 am	Meeting of the experts committee with thesis students and post-docs
12:00-12:30 am	Meeting of the experts committee with researchers *Attending: expert committee members, DS and representatives of institutions (without the direction of the unit)*
12:30-01:30 pm	Lunch
01:30-02:00 pm	Meeting of the experts committee with the head of research unit
02:00 pm	End of visit
02:00-04:00 pm	Deliberation of the experts committee (closed hearing) *Attending: expert committee members and DS*
04:15 pm	Thanks and leave of the experts committee

6 • Supervising bodies general comments

UNIVERSITÉ PARIS SUD

Comprendre le monde, construire l'avenir®

Le Président de l'Université Paris-Sud

à

Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
AERES
20, rue Vivienne
75002 Paris

Orsay, le 9 juillet 2014

N/Réf. : 153/14/JB/LM/AL

Objet : Rapport d'évaluation d'unité de recherche
N° S2PUR150008625

Monsieur le Directeur,

Vous m'avez transmis le 6 mai dernier, le rapport d'évaluation de l'unité de recherche « SIGNALISATION NORMALE ET PATHOLOGIQUE, DE L'EMBRYON AUX THERAPIES INNOVANTES DES CANCERS » - N° S2PUR150008625 et je vous en remercie.

L'université se réjouit de l'appréciation portée par le Comité sur cette unité et prend bonne note de ses suggestions. Nous serons en particulier attentifs à l'espace mis à disposition de l'unité.

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

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Centre de Recherche

institutCurie

AERES
Section des Unités
20, rue Vivienne
75002 Paris

Paris, le 27 mai 2014

Concerne : Rapport S2PUR150008625 – SIGNALISATION NORMALE ET PATHOLOGIQUE, DE L'EMBRYON AUX THERAPIES INNOVANTES DES CANCERS - 0753172R

Chers collègues,

En tant qu'organisme hébergeur et déposant unique des rapports des unités de recherche du site d'Orsay vague E, je vous informe avoir bien reçu en date du 6 mai 2014, le rapport d'évaluation de l'AERES sur l'unité indiquée en rubrique ***SIGNALISATION NORMALE ET PATHOLOGIQUE, DE L'EMBRYON AUX THERAPIES INNOVANTES DES CANCERS***».

Nous tenons tout d'abord à remercier les experts pour le temps consacré à la visite et le travail réalisé pour leur rapport.

Les constats et recommandations qui sont formulés dans ce document sont extrêmement précieux pour appuyer notre stratégie générale collaborative et interdisciplinaire. La reconnaissance du potentiel de cette unité à occuper une place importante à l'Institut Curie avec en particulier un apport de technologies innovantes est très encourageante. La combinaison de l'exploration des bases biologiques et génétiques des mélanomes et médulloblastomes et d'une active interaction avec les équipes cliniques de l'Institut Curie reflète une intégration sur le plan translationnel réussie des différents programmes de recherche de cette unité. Il sera important de soutenir/ renforcer les interactions avec d'autres unités et disciplines en particulier avec les forces existantes sur le site en imagerie et chimie.

De plus, en concertation avec les autres tutelles et partenaires, nous soulignons la forte implication des chercheurs de cette unité dans les activités d'enseignement en bénéficiant à la fois de l'environnement scientifique riche de Paris Saclay et bien sûr de l'Institut Curie.

Je vous prie d'accepter, Chers collègues, mes plus sincères salutations.

Geneviève ALMOUZNI
Directeur du Centre de Recherche
INSTITUT CURIE