SGC - Stress génotoxiques et cancer

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Genotoxic Stress and Cancer

GSC

Under the supervision of the following institutions and research bodies:

Institut Curie

Centre National de la Recherche Scientifique - CNRS

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. Jean-Sébastien HOFFMANN, chair of the committee

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

Evaluation report

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

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

Unit name:	Genotoxic Stress and Cancer
Unit acronym:	GSC
Label requested:	UMR
Present no.:	UMR 3348
Name of Director (2013-2014):	Ms Mounira AMOR-GUÉRET
Name of Project Leader (2015-2019):	Ms Mounira AMOR-GUÉRET

Expert committee members

Chair: Mr Jean-Sébastien HOFFMANN, University of Toulouse

Experts:

Mr Andrés AGUILERA, University of Sevilla, Spain

Ms Anna AKHMANOVA, Utrecht University, The Netherlands

Mr Pierre Antoine DEFOSSEZ, Paris 7 University (representative of the CoNRS)

Mr Pierre-Henri GAILLARD, Cancer Research Center of Marseille

Ms Ester HAMMOND, University of Oxford, UK

Mr Bertrand NADEL, Centre d'Immunologie de Marseille Luminy

Mr François PARIS, Cancer Research Center Nantes-Angers

Ms Anne WILLIS, MRC Toxicology Unit, Leicester, UK

Scientific delegate representing the AERES:

Mr Jean ROSENBAUM

Representative(s) of the unit's supervising institutions and bodies:

Ms Geneviève ALMOUZNI, Institut Curie

Mr Etienne AUGE, University Paris-Sud

Mr Pierre CAPY (representative of Doctoral School n° 426)

Mr Domenico LIBRI, CNRS

Mr Marc LIPINSKY (representative of Doctoral School n° 418)

1 • Introduction

History and geographical location of the unit

Over the last few years, the scientific expertise of the unit UMR 3348 "Genotoxic Stress and Cancer", created on January 1st 2010, focused on DNA metabolism (replication, recombination and repair) with the aim of characterizing some mechanisms maintaining genomic stability after DNA damage. The unit is located on the Orsay site of the Institut Curie Research Center, historically devoted to the broad field of radiobiology and genotoxicology, that extended the scope of its research to the domains of signalling, neurobiology and cancer over the past 6 years, and that is currently being reorganized with the objective of developing an integrated broad theme of "Biology, Radiation and Cancer" to allow the development of new original projects and giving the Orsay site an attractive identity. As part of this reorganization, the six units of the site will be restructured to form three units from 1st January 2015. Consequently, there was a need to restructure the existing Unit UMR 3348 in anticipation of the next 5-year research program with a broader research expertise in biology and radiobiology, besides the existing DNA metabolism field. The unit initially consisted of one junior and four senior teams. After the departure of one group leader, the unit recruited, following international calls, an excellent junior group leader working on genomic stability, who successfully obtained a permanent position at the CNRS (CR1) and a Young Investigator “ATIP-Avenir” grant, and an international recognized senior team working on RNA Biology. In January 2015, the dissolution of one of the unit’s founding teams is scheduled due to the retirement of its head, and the arrival of 3 new teams on radiation biology, cancer signalling and microtubule biology is planned. The proposed unit consists thus of 8 teams with broader expertise within the « Biology, Radiation and Cancer » field.

Management team

Ms Mounira AMOR-GUÉRET, the former director, will be the head of the new research unit. She is the leading expert on Bloom Syndrome in France and has made substantial contributions to improving our understanding of the molecular mechanisms underlying this disease. Ms Mounira AMOR-GUÉRET is due to retire in 2022 and therefore will not be eligible for reappointment for the following five-year term (2020-2024). The future of the Unit is already prepared as Mr Stéphane VAGNER, an internationally recognized scientist on RNA biology, is proposed as deputy director. They will be supported in their management tasks by an executive board comprising the eight team-leaders and helped by two administration secretaries.

AERES nomenclature

SVE1_LS1 Biologie moléculaire et structurale, biochimie ; SVE1_LS3 Biologie cellulaire, biologie du développement animal ; SVE1_LS7 Epidémiologie, santé publique, recherche clinique, technologies biomédicales

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	4	6
N2: Permanent researchers from Institutions and similar positions	9	8
N3: Other permanent staff (without research duties)	8	7
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	2	
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	10	19
N6: Other contractual staff (without research duties)		2
TOTAL N1 to N6	**33**	**42**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	6	
Theses defended	14	
Postdoctoral students having spent at least 12 months in the unit*	7	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	9	14

2 • Assessment of the unit

Strengths and opportunities related to the context

The novel structuration of the unit will add to the existing "genome stability maintenance" teams 1,2,5,7, four novel expertise: Cellular signalling and oncogenesis in leukemia provided by team 3, Radiobiology and epidemiology by team 4, Microtubule Dynamics and new aspect of cell cycle by team 6, and RNA Biology by team 8. This will lead to novel and original research lines and concepts, impulse dynamic innovation and creativity, in perfect adequation with the global strategy of the Institut Curie in Orsay. The excellent quality of the scientific animation within the unit will facilitate the emergence of these innovative research lines. This will also provide the unit with powerful and novel technical and methodological expertise (biochemistry, cell imaging, animal models, bioinformatics) besides the well-established cutting-edge technical platforms. The five-year research plan of the unit is of general very good scientific value, with potential innovative collaborative works within the units as well as with teams of the Curie Institute Orsay and Paris sites, including hospital departments for translational research. The researchers working in the unit have the required scientific and technical skills to conduct cutting-edge research.

Weaknesses and threats related to the context

An effort should be made to recruit junior groups and to hire appropriate staff to meet the challenges in terms of bioinformatics and biostatistics within the scientific strategy of the Orsay site. An effort should be made also to better exploit the intellectual property of the research conducted in the unit (e.g., only 4 patents were registered over the last 5 years for the 8 teams). The average scientific production is good, but the general quality of the research lines as well as the potential novel scientific niches will have to be translated into higher impact and better visibility publications in order to strengthen the unit's scientific reputation.

Recommendations

The unit should use the opportunity of its reorganization and of implementing new research topics (RNA Biology; Biology of microtubules; radiobiology) and technologies (Biochemistry, cell imaging, animal models) to develop innovative research lines together with the genomic stability and DNA damage response fields. This will increase the rate of high-ranking scientific publications and the international visibility.

3 ● Detailed assessments

Assessment of scientific quality and outputs

Assessment of the scientific production of the previous teams of the unit shows a total of 58 publications in peer-reviewed scientific journals over the last 5 years, some of these in-house publications being published in high-ranking scientific journals such as Mol Cell, PLOS Genet, PNAS, Nature Com. The teams that recently joined the unit or will join the unit in 2015 show also outstanding/excellent publications over the 5 last years (Cell, NSMB, Genes & Dev, Mol Cell, J Cell Biol, Nature Immunol, Leukemia, Blood) and good translational activities. The future unit, that will combine excellent expertise in different fields relevant for oncogenesis and cancer progression (genome stability, RNA biology, Microtubule biology, signalling and radiobiology) will gain in unexplored innovative research, further improving the scientific quality.

Assessment of the unit's academic reputation and appeal

The recruitment of a junior ATIP/Avenir with foreign students demonstrates the good unit's academic reputation. However, despite the good level of publications and the quality of the research lines, the previous unit globally has not gained yet sufficient international reputation. This will be certainly improved, notably by the excellent international visibility provided by the new teams recently arrived or that will join the unit.

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

There is a strong interaction with the social, economic and cultural environment, thanks to the scientific popularization (e.g., public lectures and web sites, interviews for the press and radio, documentary movies and videos, lab visits and opening to the public), the achievement of several contracts with charities and pharmaceutical/industrial companies (FRM, Fondation Avenir, EDF, Novartis, Adipogen) and the development of translational research (setting-up of cohorts in radiobiology epidemiology).

Assessment of the unit's organisation and life

The decision-making structures and animation activities of the unit are well-organized. There is a strong cohesion between researchers, engineers, technicians, and students working within the unit, as illustrated by the regular lab, unit and retreat meetings.

Assessment of the unit's involvement in training through research

There is a strong and supportive relationship between PhD students, postdocs and senior researchers in the unit, thanks to regular lab meetings, so that the monitoring of the research activities of students/postdocs is efficient. Additionally, students/postdocs are strongly encouraged to attend national and international meetings where they can present their work to the scientific community. The environment for students/postdocs is good but could be further improved by uniformly using English during the unit seminars, and making intra-unit communications in French and English. Generally, there is a general need for the unit to hire more PhD students. One strategy would be that team leaders could take a more active part in university education, especially at the three “Ecoles doctorales”.

Assessment of the strategy and the five-year plan

The five-year research plan of the unit is of high scientific value and the researchers working in the unit all have the required scientific and technical skills to conduct cutting-edge research. Importantly, there is a unique opportunity to unveil innovative research lines involving different scientific fields, thereby putting this project in the forefront of cancer biology. From a global Institut Curie strategic viewpoint, there is a strong opportunity for scientific and technical interactions with the two other units within the Orsay site, as well as with teams of the Paris site.

4 • Team-by-team analysis

Team 1 : Genetic Instability and Carcinogenesis

Name of team leader: Ms Mounira AMOR-GUÉRET

Workforce

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

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	4	
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 made novel and original discoveries in the very competitive field of the cancer-prone Bloom syndrome and its related deficient BLM DNA helicase. The observation that BLM deficiency leads to a cytidine deaminase (CDA) defect causing a pyrimidine pool imbalance has a real impact in the Bloom syndrome field and has been published in 2011 in a leading scientific journal (Nature communications). In the last 5 years, in addition to the Nat. Commun. contribution, the team has produced other papers, the latest in PLoS One 2012, and few others in highly specialized journals. The production of the group seems to be decreasing or at most is stable. In the previous 5-year (2003-2008) period the group published 1 NAR, 1 Cancer Res as senior authors, plus 1 EMBO J. and 2 NAR as collaborations, plus others. The hypothesis that CDA deficiency itself leads to cancer predisposition is a relevant and novel issue in the cancer research field, with potential for high-impact publications and future research. The group has also reported a new location and function of the helicase at centromeres. The PI, who is also the Director of the unit, is the leading expert on Bloom syndrome in France who initiated important translational developments of molecular diagnosis methods at the Curie Hospital. The team is perhaps not quite as productive as would be expected and this is likely to reflect a number of factors including the competitivity in the Bloom field, the large number of additional responsibilities of the PI as result from her role, and the relatively small size of her team.

Assessment of the unit's academic reputation and appeal

The PI has been a reviewer for many good journals (Cancer Res., Oncogene, NAR, J Cell Sci,..), a member of several important national scientific/steering committees but, despite substantial progress and novelty of the research line of her group, and probably because of the highly competitive Bloom syndrome field, invitations to speak at international conferences are missing; the group has not gained yet an international reputation.

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

The team shows important effort for the interaction with environment outside the direct scientific field, such as large public conferences and events, contribution to the NIH web page on Bloom syndrom, movies, videos and interviews.

Assessment of the unit's organisation and life

The size of the current team is relatively modest to achieve the important research outcomes; there is only one researcher with permanent position, the PI, with important administrative responsibilities, 2 Post-doc researchers (one with bioinformatics expertise), 2 engineers and 1 PhD student. The team would gain in hiring another permanent researcher and in consolidating, at the unit level, the position of the post-doc researcher with bioinformatics expertise.

Assessment of the unit's involvement in training through research

The team has provided a good training environment for 4 PhD students and 4 master students. At present, there are 2 postdoctoral fellows, 1 PhD student, and 1 master student. It is also actively involved in training through participation in teaching at the master, PhD and medical school levels at several leading institutes and universities in Paris.

Assessment of the strategy and the five-year plan

The project builds up on the previous findings and relies on the importance of CDA deficiency in several aspects of cancer biology, from the mechanisms of genetic instability to the use of biomarkers in clinic. The strategies included powerful, adequate and complementary approaches (synthetic lethal interactions through microarrays and genome-wide RNAi screen, cell imaging and biology of DNA Repair, CDA mouse models and identification of molecules specifically targeting CDA deficient tumor cells). This 5 year ambitious programme could be a concern regarding the size of the team, however, it relies on interesting preliminary data as well as important and adequate collaborations with teams and platforms within the units as well as Paris area.

Conclusion

- **Strengths and opportunities:**
  - Original research line in a highly competitive field;
  - Multidisciplinary approaches, from basic science to translational research;
  - Promising innovative project in collaboration with team 6;
  - Some projects addressing mechanistic aspects have the potential to lead to excellent publications;
  - Potential prognostic and therapeutic implication;
  - Adequate collaborations with several teams and platforms, especially within the unit and within the Orsay site.

- **Weaknesses and threats:**
  - The size of the team might be insufficient;
  - The PI has many responsibilities and is due to retire in 2022;
  - Lack of a clear bioinformatic support.

- **Recommendations:**
  - The team would need to be strengthened by recruiting a permanent researcher;
  - The team would benefit from a Bioinformatics/Biostatistics platform within the unit;
  - Provided the high competitiveness in this area of research, the group should consider to make more multidisciplinary approaches that give them collaborative opportunities with clinicians. It might be necessary to identify a co-worker in the group who could lead in addition to the PI, and take over the project for the long-term future;
  - Care should be taken to best deal with the BLM issue of research and prepare the ground to try and publish the recent work in a prominent journal.

Team 2 : Homologous Recombination and Cancer

Name of team leader: Ms Aura CARREIRA

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	3
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		
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		1

• Detailed assessments

Assessment of scientific quality and outputs

This junior research team was established just over three years ago, in October 2010 on an ambitious research program. Two papers have been published by the PI since the team was created. One publication in PNAS was essentially a follow up from her postdoctoral projects. This work defines two classes of BRC repeats in BRCA2 that have different but complementary activities that promote RAD51-mediared strand exchange. It should be mentioned that the team leader has made some major contributions to the BRCA2 field during her postdoc resulting in a paper published in Cell in 2009 where she is first author and a paper published in Nature in 2010 where she is second author out of 3 authors in total. The team leader, with a postdoctoral fellow of the team, is co-author of a review article that has just been published in the journal Human Mutation. This review is directly related to one of the research goals of the team and provides an overview of the assays that are currently utilized for studying missense variants in BRCA2.

In addition to these recent publications, there is a manuscript in preparation on work carried out in collaboration with the PI's post-doc mentor where the team leader is corresponding author. This work describes BRCA2 as a universal mediator of mitotic and meiotic recombination.

Several other projects that have been undertaken by the team are currently described as "in progress" and will hopefully soon allow the team to publish results from their "in house" studies.

Assessment of the unit's academic reputation and appeal

This young PI has made some key contributions to the field of DNA repair and recombination as a postdoctoral fellow and has gained international exposure and reputation. This combined with the worldwide reputation of the Institut Curie certainly explains the ability that the team has had to attract international postdocs and students. Although young, the team attracted 3 international post-docs and one international PhD, and the PI starts to be invited as selected speaker to national and international conferences such as the 3R meeting in 2013. Moreover, the team is a member of an international consortium investigating BRCA germline mutant alleles.

The team has benefited from solid funding after it was awarded three highly competitive grants with an FRM amorçage jeunes équipes 2011, a Marie Curie Career Integration Grant (2011) and primarily an ATIP-Avenir grant since 2011. There is funding for another 2 years with one year left for the ANR-ATIP and two years left for the Marie Curie CIG. There is also one pending application where the team is one of several partners.

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

The team leader plays an active role in the organization of several scientific events. The team leader co-organizes with three other researchers of the department a monthly DNA repair and Cell-Cycle forum. She was a co-coordinator of a symposium for young researchers that was co-organized by the Institut Curie and the Gray Institute (Oxford).

The research topic of the team was also presented to a "general public" audience after it was awarded funding by the FRM.

Part of the research concerns translational research (clinical unclassified variants; new therapeutic tools) and may have important consequences for clinical application.

Assessment of the unit's organisation and life

The young PI is the only permanent researcher. Addition of another permanent staff scientist would strengthen the group since the current team composition relies exclusively on junior temporary researchers. However, considering that this is a young team it would be best that the team recruits a permanent staff scientist at the level of IE or AI rather than CR to ensure that the team has all latitude to develop. The team would also benefit from the employment of a scientist with bioinformatic expertise at the department level.

Assessment of the unit's involvement in training through research

The team is involved in training 1 PhD, 2 L3 and 1 M1. The PI teaches in 2 international PhD courses at Curie Institute.

Assessment of the strategy and the five-year plan

The proposed works builds on existing strengths of the team and follows original and important lines of exploratory research (revealing new functions of BRCA2; classify high-risk related BRCA2 variants; exploring cancer predisposition of BRCA2 heterozygosity; exploit BRCA2-derived molecules for novel therapeutic strategies) with adequate and powerfull methodological approaches.

The different sub-projects while closely related are not mutually inter-dependent. Therefore, each line of research has the potential to yield important results on its own.

This is an ambitious research plan and one might question the ability of this small team to reach its goals within the next 5 years. However, the relevance of each line of research and the experimental strategies are well described and benefit from collaborations with other teams at the Institut Curie that have complementary expertise to that of team 2, as well as several ongoing international collaborations, which should help compensate the relatively small size of this junior group.

Conclusion

- **Strengths and opportunities:**
  - Excellent scientific background of the young PI;
  - Original and important basic and translational research lines;
  - Attractive for foreign young researchers;
  - Adequate and important collaborations with local (unit, Curie-Orsay, Curie Paris) and international research teams and platforms;
  - Potential for high-impact publications and future research.

- **Weaknesses and threats:**
  - Relatively small team given the extent of an ambitious research plan and a strong international competition;
  - Lack of publications from the team;
  - Lack of permanent staff other than the team leader;
  - Although the team has benefited from solid funding over the last three years, it has funding for another two years and needs to apply for additional funding soon to avoid a gap in financial support;
  - Highly competitive field for this young team with modest size;
  - Limited Bioinformatics and Genomics support and skill for efficient development of the project.

- **Recommendations:**
  - Young ATIP/AVENIR Team created in 2010 that would need to start to publish in 2014 for future grants and visibility;
  - The PI needs to get her HDR for independent responsibility of PhD students;
  - The team needs to receive support with the appointment of a permanent technical staff;
  - Would benefit from a bioinformatics facility at the level of Curie-Orsay.

Team 3 : Cellular Signaling and Oncogenesis

Name of team leader: Mr Jacques GHYSDAËL

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	1	1
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2
N6: Other contractual staff (without research duties)	1,5	1,5
TOTAL N1 to N6	**5,5**	**5,5**

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

• Detailed assessments

Assessment of scientific quality and outputs

This team has been investigating oncogenic transformation, especially in the context of leukemia, for many years. The team was previously on the same site, Institut Curie-Orsay, but belonged to a different research unit, which is no longer operating. The team, therefore, asks to join the unit headed by Ms Mounira AMOR-GUÉRET.

The laboratory has made important scientific contributions in a particularly competitive field, including the seminal finding and characterization of the role of the Calcineurin/NFAT signaling pathway in several lymphoid malignancies, including T-cell acute lymphoblastic leukemia (T-ALL). In the evaluated period, the team has produced 9 articles, including 4 in which team members are senior authors (2x Leukemia, 2x Plos One), and 3 book chapters. They also contributed to studies of particularly high impact (Nat Immunol, Cell Report).

Assessment of the unit's academic reputation and appeal

The team's head is internationally known for its expertise in the Calcineurin/NFAT signaling pathway in T-ALL, and has been regularly invited to chair and/or talk at international meetings. He coordinates a national network (INCa). The unit has attracted domestic as well as foreign graduate students, and post-doctoral fellows. The team leader is a member of several national and international funding agencies (FRM, Ligue Régionale, Cancéropole Île-de-France). The team has obtained significant and regular funding for his work (Labelisation Ligue, several INCa contracts, Fondation de France, Marie Curie ITN). This has allowed to build critical mass. A slight downsizing has been initiated in the perspective of the lab head's retirement by the end of the next term.

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

The research activity of the team is devoted to translational research with the aim of finding new therapeutic tools for haematological disorders. This applied research will have direct consequences for socio-economic and health issues. Interaction with the industry (Novartis, Nerviano) is ongoing (research partnership on preclinical models).

Assessment of the unit's organisation and life

Appropriate management of the team (lab meeting, J club, ..) comprising researcher, post-doc and students.

Assessment of the unit's involvement in training through research

The team leader coordinates and teaches in the Master 2 "Normal and Pathological Cellular Signalling" European M2 of Genetics, and Ecole Doctorale Biologie et Biotechnologies, University P7. He also participates to the initial training network (HEM_ID, EU).

The lab is involved in training of Master students, graduate students and post-doctoral fellows. 4 PhD students have graduated during the evaluation period.

Assessment of the strategy and the five-year plan

Much of the proposed work builds on existing strengths and past activity of the laboratory, and includes a recent line of exploratory research. These will address key questions in lymphocyte development and control with potential translational impact in the understanding of disordered lymphocyte function and malignancy. In support of these goals a number of valuable experimental models, including functional genomic approaches and various in vitro and in vivo models have been established to determine the key role of defined signalling pathways and their underlying genetic control. These models are well established in the group and likely to be highly productive. The dissemination of these approaches to other groups in the Unit will add particular value.

Theme 1: decipher the fundamental mechanisms underlying Calcineurin/NFAT function in T-ALL and determine the therapeutic value of targeting the Frizzled/wnt pathway. This theme constitutes the core activity and renowned expertise of the lab. Based on their recent demonstration in mice of the involvement of the Calcineurin/NFAT signalling pathway in T-ALL leukemic initiating cell (LIC) activity, the team aims to further dissect the hypothesis that

this pathway is triggered by Wnt ligands present on stromal cells from the microenvironment, and test whether Wnt receptors (frizzled) might constitute actionable targets to inhibit T-ALL LIC activity. An effort is ongoing to validate the previous discoveries from mouse models to human T-ALL. Functional experiments will be conducted in parallel in established mice models and human primary samples, in particular through the use of T-ALL xenografts and lentiviral-based genetic modifiers (shRNA..) and trackers (GFP..). This combination of ex vivo/in vivo and human/mouse approaches is currently the state-of-the-art in pathway/target validation in oncology, and has good chance of success. A second line of investigation concerns the identification of molecular events mediating LIC activity downstream of calcineurin in T-ALL cells, and is approached through a combination of expression profiling mouse genetics and proteomics. This approach is complex due to the hub nature of calcineurin and functional redundancy of downstream effectors (NFAT), and is by nature more risky.

Theme 2: investigate the function of Calcineurin/NFAT signaling in breast cancer. This is a recent research line in the lab, and is conducted conjointly with a laboratory at the Centre de Recherche en Cancérologie de Marseille that will carry the required expertise in the breast cancer field. As the Calcineurin/NFAT signaling module is a ubiquitous pathway not restricted to T-cells, the joint labs will further investigate preliminary data using cell lines suggesting a potential role in local tumor survival and metastasis. Upon validation of differential expression of effectors in breast cancer subtypes, functional investigation will be carried-out using an orthotopic graft model of breast cancer already established in the Marseille laboratory. This research line opens an interesting new angle of the exploration of the role of the Frizzled/wnt/b-catenin pathway in breast cancer.

Theme 3: decipher the fundamental mechanisms of IKAROS tumor suppressive function in B-ALL. This research line builds on the previous finding (performed in collaboration with a laboratory at the Institut de Génétique et de Biologie Moléculaire et Cellulaire. (Strasbourg), expert in the IKAROS field) that IKAROS deficiency accelerates tumorigenesis in a mouse model of BCR-ABL+ B-ALL, in line with the poor prognosis associated with IKZF1 haploinsufficiency in human B-ALL. The team aims to further validate functionally a set of candidate genes identified through differential profiling, using the same type of mouse genomics and pharmacology approaches on xenografts described in theme 1, and again with reasonable chances of success. The long-term goal is to explore new therapeutic targets responding to unmet medical need.

Most of the lab efforts will be devoted to theme 1 in the next period, with the lead on the 2 other themes progressively terminated or passed to collaborators.

Conclusion

In conclusion, the research program builds on solid scientific grounds and state-of-the-art tools with a good balance between fundamental and translational research. Most aspects of the proposed 5-year strategy have high likelihood of success, with few more risky components. A wise strategic focus has been anticipated in the perspective of the coming retirement of the team leader.

- **Strengths and opportunities:**
  - Long history of important publications. Long-standing implication in the field of transformation and leukemia.
  - State-of-the-art experimental approaches combining mouse genomics and functional pharmacology in xenografts, in the frame of an excellent scientific and intellectual translational research environment combining researchers and clinicians.
  - The laboratory has shown ability to secure funding from various sources.
  - Potential of dissemination of the lab's know-how (animal pre-clinical modelling, translational research) to other teams of the unit.

- **Weaknesses and threats:**
  - Publication record is not optimal relative to the high quality of the work produced, weakening international visibility.
  - Low pool of staff with HDR to drive PhD students
  - The future of the technical staff dedicated to animal care is currently uncertain.
  - Threat of isolation. Care should be taken to integrate in and benefit from the new unit.

- **Recommendations:**
  - Enhance visibility by increasing the production of high impact publications with team members at strategic positions.
  - Securing current staff for animal experimentation is of great mutual interest both for the team and for the whole unit
  - The team must carefully consider how to bring mutual added value with other teams of the unit, and define how to reach common academic and translational objectives.

Team 4 : Radiosensitivity and Cancer Risk

Name of team leader: Ms Janet HALL

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	2
N3: Other permanent staff (without research duties)	1	
N4: Other professors (PREM, ECC, etc.)	1	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**8**	**4**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	7	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

As part of the reorganization of the Orsay site, the single team unit directed by the PI of team 4 will join the present unit in January 2015. The team is one of the few French expert teams in Radiobiology and the scientific quality of its expertise is internationally recognized. Its main goal is to validate genes involved in radiosensitivity through both molecular epidemiology and biochemistry approaches. The scientific production is constant, on average 5-7 papers per year, mostly in specialist journals relevant to the field of radiobiology. Among the 24 articles published since 2009, 9 include lab members as first or senior authors.

Assessment of the unit's academic reputation and appeal

The team's PI is internationally known for its expertise in epidemiology of radiosensitivity. She is the Curie Institute moderator for the European Program DoReMi in EURATOM and the Inserm representative on the French Committee for EURATOM. Her work is funded by 3 EC grants and several domestic grants. The unit has attracted French as well as foreign graduate students, and post-doctoral fellows. A high number of the team papers are the result of collaborations (both local and international), which the committee believes reflects PI' standing in the field. The team leader is regularly invited to international meetings or to sit on committees.

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

The team has several interactions with medical organizations (contribution to workshops, working groups).

Assessment of the unit's organisation and life

Not applicable since the team will arrive in the present Unit in January 2015.

Assessment of the unit's involvement in training through research

Over the past 5 years, 5 students completed their PhDs and 3 are still in progress. The team included a high number of student international trainees with a short term fellowhip. The PI is heavily involved in teaching and training and is well known internationally for her involvement in European consortium, such as DOREMI.

Assessment of the strategy and the five-year plan

The strategy for the group has two broad aims, firstly a molecular epidemiological approach to determine the role of genetic variations in radiation sensitivity and secondly a molecular and cellular approach to investigate the role of Cdk5, linked to the post-translational modification of PARP and XRCC1, in radiation sensitivity. The team would benefit from a stronger connection between these two projects. The identification of cdk5 dependent phosphorylations on PARP-1/2 and XRCC1 has already resulted in a publication and should be fully investigated. Access to a significant amount of clinical material is available to support both aims, some of which are only just ready for use having taken a considerable amount of time to collect. The PI is clearly well connected and placed to make use of such cohorts. A chemical screen is proposed to identify cdk5 inhibitors, with the use and expertise of the Curie Institute chemical library. These projects have the potential to generate high-impact future translational research and good publications and will be of great interest to the field.

Conclusion

- **Strengths and opportunities:**

International visibility in radiobiology. Excellent and recognized expertise in molecular epidemiology. The PI is well-connected and involved in a large number of European collaborative projects. The unit will benefit from the arrival of this team developing translational research that will be complementary to the basic research teams. Interaction with another team in the unit on quadruplex p53mRNA already shows one of the potential synergies. The

team is well positioned to take advantage of clinical samples suitable to address the key questions. Because of the new radiotherapy treatments and functional imaging screening, the result of the projects will provide major societal advices. The team has the ability to investigate the most modern of radiotherapy techniques is also a great strength (the use of protons for example).

- **Weaknesses and threats:**

The PI has many interests spread over a number of disease types ranging from breast cancer to Huntington's and a large number of radiation protocols complexifying the main project and making the publication of high impact papers on any one subject harder. The size of the team might be also insufficient to achieve the objectives.

- **Recommendations:**

The team must be careful not to overestimate the number and complexity of projects in function of its human resource.

The molecular and cellular research has to be supported and better linked to the epidemiological project.

Team 5 : Oxidative Stress, Redox Regulation and Cell Fate

Name of team leader: Mr Meng ER HUANG

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	2	1
N3: Other permanent staff (without research duties)	3	2
N4: Other professors (PREM, ECC, etc.)	1	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**7**	**5**

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

• Detailed assessments

Assessment of scientific quality and outputs

The team has been investigating the involvement of reactive oxygen species in genomic instability for these recent years in different models from yeast to human cells. The qualitative production of the group is relatively modest since 2009: 10 total publications, 7 with lab members at strategic positions, including 1 PLoS Genetics (IF 9) in 2009 and 1 Mol Microbiology (IF 5) in 2011. One of the likely reasons is that the team is a relative newcomer to the redox field, a very competitive field. The new redox sensors developed by this team for monitoring the intracellular redox state have the potential for higher impact publications and future research. The team leader has shown in the past competence to publish highly cited articles.

Assessment of the unit's academic reputation and appeal

Although well known nationally, the team leader has not travelled very widely outside of France and this has hampered his international profile. Invitations to speak at international conferences are clearly missing and the research in the redox field of the team has not yet gained an international visibility. The funding is relatively modest (Regional Ligue contre le cancer; Association Fugain, …).

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

1 patent in 2010 and 1 collaborative project with L'OREAL on essential oils.

Assessment of the unit's organisation and life

Following the closure of two other laboratories in 2008, the PI recruited 3 researchers from different fields and two of them have now retired. This unstable situation was certainly destabilizing for a team newcomer to the redox field and probably negatively impacted the research progress and publication production. The team would gain in stabilizing its organization to further develop more focalized research lines.

Assessment of the unit's involvement in training through research

The team leader is involved in PhD level teaching and he has trained 3 PhD students, one finished (in 3 years) 2 ongoing. His teaching of MSc levels students is limited.

Assessment of the strategy and the five-year plan

The research lines of the five-year plan include the regulation of DNA replication by redox mechanisms, the initiation/progression of cell death induced by oxidative species quantified by the generation of novel and powerful tools, and the synergy Redox mechanisms/ionizing radiations as a potential therapeutic approach. The development of the new redox sensors for monitoring the intracellular redox state has the potential to lead to collaborative works with the "genome stability maintenance" teams within the unit and need to be a priority in order to gain visibility in the field. The mechanistic aspects of the project regarding the regulation of DNA replication by redox processes could lead to good publications.

Conclusion

- **Strengths and opportunities:**

The team has developed a new methodology to assess and measure ROS levels and redox pairs. It is clear that significant effort has been made to set up overlapping systems that will be very informative. These capabilities will enhance collaborations both internally in its own Unit but importantly externally within the international research community. This technology may provide also the team with some exciting development in translational oncology research. The regulation of DNA replication by redox mechanism is original and need to be extrapolated to human cells.

- **Weaknesses and threats**

Production is relatively modest; unstable team organization; newcomer in a competitive field; lack of international visibility.

- **Recommendations:**

It is imperative that the team identifies a niche within this field that they can uniquely exploit. The organization of the team needs to be stabilized and the research lines need to be more focused with further refining of the specific questions. The PI needs to establish an international reputation in this field as quickly as possible through collaborations (within the unit would be the most efficient), higher quality of publications with team members at strategic positions and conference presentations. It is envisioned that the unique research tools the team has developed will allow them to increase both international collaborations and scientific profile. The internal support by the relocation into this team of a retiring team PI as an "emeritus" director should give a positive support and help to solve these points.

Team 6 : Regulation of Microtubule Dynamics and Functions

Name of team leader: Mr Carsten JANKE

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		
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.)	4	6
N6: Other contractual staff (without research duties)	1,5	0,5
TOTAL N1 to N6	**6,5**	**8,5**

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

• Detailed assessments

Assessment of scientific quality and outputs

The team pursues a highly original research line on the biochemistry and function of tubulin modifications, polyglutamylation and glycylation. This research line has a very high impact in the field, because it addresses a long-standing but still poorly understood scientific problem – how the multiplicity of the cellular functions of microtubule filaments is supported by their biochemical diversity. The team has made outstanding contributions to this topic by identifying and characterizing the enzymes responsible for the addition and removal of tubulin modifications, and used this knowledge to investigate the role of these modifications in different biological processes such as ciliogenesis, brain function and more recently, cancer. The research output of the group is of very high scientific quality: the work is published in leading scientific journals, including Cell, Developmental Cell and the Journal of Cell Biology, and is very well cited. The team also participated in original and important studies through collaborations with other leaders in the field.

Assessment of the unit's academic reputation and appeal

The team has an excellent reputation because of its unique research focus. The team leader is very well known within the community not only because of the publications, but also because he broadly distributes the reagents for studying tubulin modifications, which are widely applicable. The academic reputation of the group is further supported by numerous invitations to give presentations at national and international conferences and at different research institutions. The team leader is also a highly visible member of the microtubule community because he has set up a highly popular series of EMBO conferences on microtubules and organized several workshops. He has been selected to join the EMBO Young Investigator programme, which unites the best young group leaders in the molecular biology field in Europe.

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

The team takes appropriate effort for the interaction with environment outside the direct scientific field, for example, through coordination and fund raising for new facilities at the Orsay campus, through participation in science popularization events and through several industrial partnerships.

Assessment of the unit's organisation and life

The team has greatly grown since its move to Orsay in 2010. The current team composition represents a good mix of more senior and more junior temporary researchers, although it should be noted that addition of another permanent staff scientist would have strengthened the group and its viability. The excellent research output of the team suggests a scientifically productive and stimulating environment.

Assessment of the unit's involvement in training through research

The group is actively involved in training through lab-training of postdocs, PhD students as well as Master and early stage students, through co-organization and teaching at international PhD courses and through participation in teaching at the Master level at several leading institutes in Paris. An important feature of this team is a broad methodological diversity (from generation of mouse models to tubulin biochemistry), which provides a good basis for versatile scientific training of students and postdocs.

Assessment of the strategy and the five-year plan

The strategy of the team is to cover a very broad spectrum of topics related to tubulin modifications, ranging from in depth molecular characterization of the tubulin-modifying enzymes and cell biology of tubulin modifications to addressing the higher-order functions of these modifications by using mouse knockouts. Such an ambitious plan might be a concern, however, the team's publications demonstrate that it is very well capable to cope with a technically broad set of experimental approaches. These approaches are complementary, and together, they are clearly the way to go in order to resolve the challenging problem on the role of tubulin modifications in cell architecture and animal development.

There are already established collaborations with other teams within the unit, and the strategy to further strengthen these interactions will strongly contribute to the innovation potential and orinality of the unit. The project of this team provides an important contribution to the the scientific viablity and future development of the whole unit.

Conclusion

- **Strengths and opportunities:**
  - Original and fundamentally important research line;
  - Unique set of experimental tools;
  - Multidisciplinary approach;
  - An internationally visible PI with an excellent track record;
  - Possibilities for medically important contributions, e.g. related to cancer, neurodevelopment and neurodegeneration and ciliopathies;
  - There is excellent supportive environment within the research unit and the institute for working with genetically modified mice which will allow the team to optimally use their collection of mouse knockout models of tubulin-modifying enzymes;
  - There are exciting possibilities for establishing collaborative research lines between this team and other teams within the unit connecting cytoskeletal organisation, dynamics and modifications to DNA damage response mechanisms..

- **Weaknesses and threats:**

No significant weaknesses or threats except for the Europe-wide funding difficulties and potential issues with lab space within the institute.

- **Recommendations:**

Strong focus on the analysis of the generated mouse models and the development of biochemical tools to study the mechanistic aspects of tubulin modification, such as generation of tubulin pools with defined post-translational modification profiles, are a good strategy that should be further prioritized. Interactive innovative research lines on the connection between genotoxic stress, cancer and the cytoskeleton within the unit should receive sufficient attention.

Team 7 : DNA Recombination, Replication and Genome Stability

Name of team leader: Ms Sarah LAMBERT

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

The team has an emphasis on investigating genomic instability induced by replication stress. It is a relatively young group, initiated in 2009, that is producing good results in the last years. It seems it took some time for this group to start producing its own research material, but meanwhile was also productive in the work derived from the previous work of the team leader in UK. It is worth noticing a recent PLoS Genetics in 2012, coming entirely from this group, or a Mol. Cell, which was performed as part of a collaborative effort, where the PI is first and corresponding author, plus other collaborations, one in Genes Dev. The team has also been associated with several reviews and book chapters (3 in 2013 and 1 in 2012).

Assessment of the unit's academic reputation and appeal

As deduced from the team leader published work and, above all, her contributions as invited speaker in international meetings (4) and national meetings, or her involvement in writing reviews, no doubt that the team is building up a good reputation and, above all, the visibility necessary to foster research as a referent in the field of recombination and replication in particular using S. pombe as a model system.

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

It is under construction, consistent with the early stage of the team. The team leader has participated in activities inside I. Curie or through outside partnerships. She initiated the “DNA Repair and Cell cycle forum” that holds monthly conferences at the Institut Curie by international and national speakers. She also is a member of the academic assembly. The team has also taken part in events targeting a lay audience, such as the Web-Radio of the Curie Institute.

Assessment of the unit's organisation and life

It seems standard, even though this is a very small group that needs further interaction with other groups for a minimal critical mass.

Assessment of the unit's involvement in training through research

It is still not too strong, but it is a young group. It has 1 Thesis defended and the PI has trained Master M2 and M1 students. It may be a reasonable activity, considering the limitations of the French system to supervise PhD students and the difficulty to get Master students without being involved in teaching. The team leader has participated to several annual teaching programs and was a representative for the Curie Institute at the European MIT Fait in 2012. However, the team needs to establish better its future plans to be able to get more students in order to build a group with a competitive and minimal critical mass, in particular now that the team leader has the HDR since 2011.

Assessment of the strategy and the five-year plan

The proposed five-year research plan is built on the expertise of the team in the analysis of the molecular consequences of replication stress at the chromosomal level. There are three main lines of research that are well presented. The contribution of the different members of the team, and those to be recruited, to each of the lines of research within the research plan is clearly described.

A first goal is to continue the team’s current studies on the mechanisms of replication fork restart by homologous recombination, exploiting a powerful genetic assay that they have developed. A second project tackles the question of how homologous recombination protects cells against replication-induced genome instability. Finally, the team will expand on new results that reveal a functional link between chromatin assembly and the control of homologous recombination at challenged replication forks. Overall, it presents a realistic five-year-research plan based on well thought out experimental strategies. The small size of the team is compensated by four promising

collaborations that should allow the establishment of novel methodologies which provide original experimental strategies and limit the risks of a competitive field on a timely research topic.

The team plans on setting up mammalian cell projects that will come and complement its expertise in the use of S. pompe as an investigational tool. This will also broaden the potential of the team in terms of funding application, an important issue since additional funding will be required to achieve the proposed five-year research plan. This is a certainly important aspect that should be supported by stimulating collaborations, increase funding and enlarging the size of the group, even though the mammalian cell research needs to be better defined at this point

Conclusion

- **Strengths and opportunities:**

Young research team, with an interesting basic research project of important impact in cancer and using a model system, which provides it with a competitive advantage. The team is in a dynamic environment with other people that can interact within the Paris area. In general, the research is balanced and should give answers to important questions that are of interest to the field of genomic instability and carcinogenesis, which the team is taking advantage to develop new methodologies.

- **Weaknesses and threats**

The need to make the research line attractive enough in an environment where other groups are better oriented to cancer research demands a larger effort to avoid being isolated. The team size and funding need to increase. Lack of expertise in human cells and of biochemistry background, even though it is unclear how much of research efforts will be on Biochemistry.

- **Recommendations:**

The collaborations with other groups in I. Curie should be enhanced. The team needs now to confirm its plan to extend its research beyond S. pombe. This will not only highlight the general relevance of the research it conducts, but will also add visibility and interest for students and postdocs to join the laboratory. However, none of this will be possible without obtaining more funds. It is important that the team grows in an equilibrated manner to ensure that extension of its research to other systems does not come to the expense of the current lines of research and team's expertise.

The team should apply for funding from the main funding agencies to ensure sufficient funding after 2017, recruit postdocs that have expertise in working on mammalian cells, attract permanent CR2 or CR1 researcher with mammalian cell expertise to help develop mammalian cell projects and reduce work load on team leader.

Team 8 : RNA Biology linked to DNA damage

Name of team leader: Mr Stéphan VAGNER

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	1	1
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	3
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	2	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs

This team was previously located at Institut Gustave Roussy, in Villejuif, France and it joined the unit at Institut Curie in January 2013. The leader of this team is a research director with INSERM, and is the proposed vice-director of the unit for the coming time period. Evidently, the transition went well and the team is well-integrated into its new environment. This team is very well placed in the unit, as it gives rise to synergy: the team's knowledge of the RNA field is useful to others, while the team will profit considerably from the unit's knowledge of DNA damage.

This team had excellent outputs in the last 2-3 years. There are 2 papers in top quality journals in this field with impact factors of over 14 (NSMB and Genes and Dev) and three papers in journals that have impact factor between 8-9 which are well respected in the RNA biology/Cancer Research field namely CDD, NAR and Cancer Res.

In terms of paradigm shift, it has been proposed by the RNA Biology field that there are important links between the different stages of the gene expression pathway e.g transcription, splicing, RNA processing and translation, however there are very few studies that have examined how these processes are interrelated and coordinately regulated. The team have made significant progress in this regard particularly in collaboration with other expert labs.

1. They have shown how alternative splicing can regulate transcription.

2. That polyadenylation of specific mRNAs controls recruitment of regulatory RNA binding proteins.

3. They have also examined the link between miRNA expression and regulation of the translation, for example, by showing that the synthesis of Rho protein is controlled by HuR which regulates miRNAs.

Taken together these studies illustrate that gene expression is a continuum that consists of interlinked and co-regulated processes and not separate individual steps. This work will therefore change how many researchers regard the gene expression process.

The importance of translational initiation factors in cancer progression and metastasis has been shown in a number of systems, however there is still much which isn't fully understood. The team have made novel discoveries in this area showing a relationship between BRAF signalling and eIF4F complex formation. This could lead to new ways to chemosensitive cells to killing by therapeutic agents and in the longer term this could be of direct benefit to patients.

Finally, the group has carried out genome wide screening to examine the miRNAs that are dysregulated in mouse mammary tumour models. This work has identified some novel target miRNAs; this work is unpublished at present.

The team has been well-funded in the past, mostly by french agencies (INCa, ANR, ANRS, ARC, FRM). This has led to the recruitment of the 3 postdocs currently active in the team

Assessment of the unit's academic reputation and appeal

The group is gaining a good international reputation for their work in the protein synthesis field, although they are not known at present in the DNA damage field. The team leader has been invited to speak a 9 international conferences. He has been a member of two scientific committees agencies (INCa, Ligue Régionale). He has obtained significant funding. The team leader is involved with the local École Doctorale. He has trained 4 PhD students and 3 M2 students.

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

The team leader has helped to translate one of the most widely used texts for undergraduate/new graduate students into French (Molecular Biology of the Cell), he has participated in events involving patients on two open access days.

Assessment of the unit's organisation and life

There are 6 researchers, at a variety of stages of their careers, which should be sufficient to achieve some very positive research outcomes.

Assessment of the unit's involvement in training through research

The team provides an excellent training environment for both postdoctoral research fellows and PhD students. The researchers learn a wide range of molecular/cell biology techniques. At present there are 4 PhD students and 3 masters students in the laboratory.

Assessment of the strategy and the five-year plan

The five plan aims to build upon previous work and is divided into 3 sections:

Section 1: To examine how the post-transcriptional events are coordinated following DNA damage. This section aims to bring together large screening projects and examine how changes in splicing to allow inclusion or exclusion of 5' and 3' UTR elements in the RNAs affect the translation of the downstream mature transcripts, following DNA damage. This will be interesting and at present, as far as the committee is aware no one is carrying these important projects. This section is hugely ambitious and perhaps should be more focussed. Moreover, the types of chemical that will be used cause very different types of DNA damage and therefore they may not identify subsets of mRNAs that are regulated by all types of damage.

Section 2: The overall aim of this section is to identify the mRNA binding proteins involved in the DNA damage response. This section is more focussed as they propose to examine how hnRNPH/F interacts with the polyadenylation machinery, to use CLIPSEQ to examine the repertoire of mRNAs that bind to this protein under control conditions and following IR, and finally, how mutations effect TP53 polyadenylation. This is interesting work that will lead to high quality papers

Section 3: This is to target cells to DNA damaging agents by modifying eIF4F function. Cells will be treated with specific BRAF and MEK inhibitors and ribosome profiling will be performed to identify those mRNAs that are resistant to these compounds. In parallel they aim to determine how this phenocopies in mouse models of BRAF and finally use novel inhibitors of protein synthesis to chemosensitise cells. These series of experiments will generate interesting new data that could be translated into a clinical setting.

Conclusion

Overall this is a very strong 5 year programme that will yield interesting novel and timely data. The data obtained from the proposed research will be of importance to a number of fields including DNA damage, protein synthesis and splicing and will have benefit to patients in the longer term.

- **Strengths and opportunities:**

The strength is that the team plans to integrate data sets from both splicing and translation analysis. Very few laboratories are carrying out this type of research and this therefore gives the Wagner group a competitive edge over others working in this area. The focussed projects listed in sections 2 and 3 are excellent and will lead to excellent publications. The research to identify novel inhibitors of eIF4A could ultimately lead to new ways in which to chemosenstise patients to a range of treatments and, in the longer-term, would be of interest to industry and other related stakeholders.

- **Weaknesses and threats:**

The first section of proposed research, in the opinion of the committee, slighty lacks focus as a number of different DNA damaging agents are discussed e.g. cisplatin, topo II inhibitors, etoposide etc. It is proposed that changes in splicing, translation, the RNA binding protein repertoire and cell signalling regulation will be carried out for a range of compounds. This is a huge task and while completely worthwhile it is too much work for the size of the resource requested. Although no one, to the committee's knowledge, is working on the link between splicing and translation and DNA damage, other groups are carrying out research into the impact of translational control on the

DNA damage response and more specifically on how RNA binding proteins control the DNA damage response. Analysing such large data sets (even from just one type of DNA damaging agent) will require very complex bioinformatics and this could also represent a significant challenge (as pointed out by the team leader himself).

- **Recommendations:**

It would probably be better to focus section 1 a little more and just to use one type of DNA damage e.g TOPO II inhibitors rather than spread the resource allocated too much. It is important to concentrate on the link between splicing and translation which is proposed as this gives the group a strong competitive advantage over others working in this field. The team leader should consider writing a grant application for an experienced bioinformatician for his team to deal exclusively with the large data sets that are being generated.

5 • Conduct of the visit

Visit dates:

Start: February 4th, 2014 at 9 am

End: February 5th, 2014 at 4 pm

Visit site: Institut Curie, Orsay

Conduct or programme of visit:

4 February 2014	
08.45-09.00 am	Welcome coffee with Team Leaders ***(polyvalente room – building 111)***
09.05-09.35 am	Welcome (closed-door) visiting committee with the AERES Scientific advisor **Closed session** ***(meeting room – building 111)***
09.40-09.55 am	**AERES representative**: The role and procedures of AERES ***(amphitheater – building 111)***
10.00-11.00 am	**Director of the Unit** (presentation, discussion): Presentation of the past activities and Project ***(amphitheater – building 111)***
11.05-11.20 am	Coffee break ***(polyvalente room – building 111)***
11.25-12.05 pm	**Team 1 – Genetic Instability and Carcinogenesis** – Ms Mounira AMOR-GUÉRET (Senior PI) ***(amphitheater – building 111)*** (Talk + discussion + time with the team leader + time for committee)
12.10-12.40 pm	**Team 2 – Homologous Recombination and Cancer** – Ms Aura CARREIRA (Junior PI – ATIP Avenir) ***(amphitheater – building 111)*** (Talk + discussion + time with the team leader + time for committee)
12.45-01.45 pm	Lunch and Posters ***(polyvalente room – building 111)***
01.50-02.35 pm	**Parallel meetings with personnel** Discussions with engineers, technicians, administrative ***(room 210 – building 110)*** Discussions with staff scientists ***(room 113 – building 110)*** Discussions with students and post-docs ***(amphitheater – building 111)***
02.40-03.20 pm	**Team 3 – Cellular Signaling and Oncogenesis** – Mr Jacques GHYSDAEL (Senior PI) ***(amphitheater – building 111)*** (Talk + discussion + time with the team leader + time for committee)

03.25-04.05 pm **Team 4 - Radiosensitivity and Cancer Risk** – Ms Janet HALL (Senior PI)
(amphitheater - building 111)
(Talk + discussion +time with the team leader + time for committee)

04.10-04.25 pm Coffee break
(polyvalente room - building 111)

04.30-05.10 pm **Team 5 - Oxidative Stress, Redox Regulation and Cell Fate** – Mr Meng ER HUANG (Senior PI)
(amphitheater - building 111)
(Talk + discussion + time with the team leader + time for committee)

05.15-06.05 pm **Team 6 - Regulation of Microtubule Dynamics and Functions** – Mr Carsten JANKE (Senior PI)
(amphitheater - building 111)
(Talk + discussion + time with the team leader + time for committee)

06.10-07.10 pm **AERES committee:** Debriefing on the team presentations **Closed session**
(meeting room - building 111)

5 February 2014

09.15-09.30 am Welcome coffee with Team Leaders
(polyvalente room - building 111)

09.35-10.15 am **Team 7 - DNA Recombination, Replication and Genome Stability** – Ms Sarah LAMBERT (Junior PI)
(amphitheater - building 111)
(Talk + discussion + time with the team leader + time for committee)

10.20-11.00 am **Team 8 - RNA Biology linked to DNA damage** – Mr Stéphan VAGNER (Senior PI)
(amphitheater - building 111)
(Talk + discussion + time with the team leader + time for committee)

11.05-11.20 am Coffee break
(polyvalente room - building 111)

11.25-11.55 am Discussion with the representatives of the **managing bodies Closed session**
(meeting room - building 111)
Ms Geneviève ALMOUZNI, Institut Curie
Mr Thierry GRANGE, CNRS
Mr Etienne AUGÉ, University Paris 11

12.00-12.15 pm Discussion with the representatives of **"Ecoles doctorales" Closed session**
(meeting room - building 111)
Mr Pierre CAPY, 'Gènes, Génomes, Cellules'
Mr Marc LIPINSKI, 'Cancérologie '
Mr François SIGAUX, 'Biologie et biotechnologie'

12.15-12.45 pm Discussion with the head of the Unit (if necessary) **Closed session**
(meeting room - building 111)

12.50-03.50 pm **Private meeting of the visiting committee (in presence of the AERES scientific advisor) Closed session**
(meeting room -building 111)
Lunch will be provided on site

04.00 pm **End of the visit**

Specific points to be mentioned:

Ms Ester HAMMOND could not attend the site visit, but produced a written report.

6 • Supervising bodies' general comments

Centre de Recherche

AERES
Section des Unités
20, rue Vivienne
75002 Paris

Paris, le 10 avril 2014

Concerne : Rapport S2PUR150008620 - STRESS GENOTOXIQUE ET CANCER - 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 le rapport en date du 21 mars 2014, le rapport d'évaluation de l'AERES sur l'unité indiquée en rubrique « Stress génotoxique et cancer ».
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. La reconnaissance de l'apport de nouvelles expertises dans le cadre de la nouvelle proposition est très encourageante.

En concertation avec les autres tutelles et partenaires, nous avons bien noté les recommandations de ce comité pour profiter de la nouvelle structuration de l'unité et ainsi développer de nouveaux thèmes de recherche et de nouvelles technologies. Ces développements permettront de renforcer une recherche innovante et collaborative en lien avec le domaine de la stabilité du génome et la réponse aux dommages de l'ADN. Ces aspects seront encouragés.

Nous soutenons vivement l'objectif important mentionné par le comité de recruter des équipes juniors et du personnel technique pour adresser les défis de bioinformatique et biostatistique sur le site d'Orsay en cohérence avec les autres sites de l'Institut Curie en bénéficiant de l'environnement scientifique riche de Paris Saclay et bien sûr de l'Institut Curie dans sa nouvelle politique de recrutement global sur le site afin de favoriser les collaborations.

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

Geneviève ALMOUZNI
Directeur du Centre de Recherche
INSTITUT CURIE