IRCM - Stabilité génétique, cellules souches et radiations

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Institute of Cellular and Molecular Radiobiology

iRCM

Under the supervision of the following institutions and research bodies:

Université Paris 7 – Denis Diderot

Institut National de la Santé Et de la Recherche Médicale

Commissariat à l'Énergie Atomique et aux Énergies Alternatives

Université Paris-Sud

January 2013

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

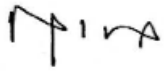
Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head



Pierre Glaudes

The president of AERES "signs[...], the evaluation reports, [...]countersigned for each evaluation department by the relevant head of department (Article 9, paragraph 3, of french decree n°2006-1334 dated 3 november 2006, revised).

Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).
This score (A+, A, B, C) concerned each of the six criteria defined by the AERES.
NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

Criterion 1 - C1 : Scientific outputs and quality ;
Criterion 2 - C2 : Academic reputation and appeal ;
Criterion 3 - C3 : Interactions with the social, economic and cultural environment ;
Criterion 4 - C4 : Organisation and life of the institution (or of the team) ;
Criterion 5 - C5 : Involvement in training through research ;
Criterion 6 - C6 : Strategy and five-year plan.

With respect to this score, the research unit concerned by this report and its in-house teams received the following grades:

- Grading table of the unit: Institute of Cellular and Molecular Radiobiology iRCM

C1	C2	C3	C4	C5	C6
A	A	A+	A	A	A+

- Grading table of the team 1: Development of the gonads (LGD)

C1	C2	C3	C4	C5	C6
A	A	A+	A	A+	A

- Grading table of the team 2: Gametogenesis, apoptosis, genotoxicity (LGAG)

C1	C2	C3	C4	C5	C6
A	A	A	B	A	A

- Grading table of the team 3: Molecular Pathways implicated in the expansion and transformation of human hematopoietic stem and progenitor cells (LSHL)

C1	C2	C3	C4	C5	C6
A+	A	A	A	A	A+

- Grading table of the team 4: Neural stem cells and radiation (LCNNC)

C1	C2	C3	C4	C5	C6
A	A	A	A	A	A

- Grading table of the team 5: Repair and transcription in stem cells (LRTS)

C1	C2	C3	C4	C5	C6
A+	A+	A+	A	A	A+

- Grading table of the team 6: Keratinocyte stem cells, regenerative potential and genomic stability (LGRK)

C1	C2	C3	C4	C5	C6
A	A	A+	A	A	A

- Grading table of the team 7: Genetic instability (LRIG)

C1	C2	C3	C4	C5	C6
A	A	A	A	A	A+

- Grading table of the team 8: Genetic and molecular radiobiology (LRGM)

C1	C2	C3	C4	C5	C6
A	A	A	B	B	A

- Grading table of the team 9: Repair and ageing (LREV)

C1	C2	C3	C4	C5	C6
A	A	B	A	A	A

- Grading table of the team 10: DNA repair and nuclear dynamics (LDNR)

C1	C2	C3	C4	C5	C6
NN	NN	NN	NN	NN	A+

- Grading table of the team 11: Telomeres and chromosome repair (LTR)

C1	C2	C3	C4	C5	C6
A+	A	A	A	A	A+

- Grading table of the team 12: Functional genome exploration (LEFG)

C1	C2	C3	C4	C5	C6
B	A	A	B	B	B

Evaluation report

Unit name:	Institute of Cellular and Molecular Radiobiology
Unit acronym:	iRCM
Label requested:	UMR S
Present no.:	UMR S967
Name of Director (2012-2013):	Mr Paul-Henri ROMEO
Name of Project Leader (2014-2018):	Mr Paul-Henri ROMEO

Expert committee members

Chair:	Mr Philippe PASERO, IGH, Montpellier
Experts:	Ms Agnes BERNET, Centre Léon Bérard, Lyon, (representative of the CNU)
	Ms Elizabeth COHEN-JONATHAN MOYAL, ICR, Toulouse (representative of CSS INSERM)
	Mr Frédéric COIN, IGBMC, Strasbourg
	Mr Gilles FAVRE, ICR, Toulouse
	Mr Paul FOWLER, University of Aberdeen, Scotland
	Mr Jean-Marc LEMAITRE, IGF, Montpellier
	Mr Joachim LINGNER, EPFL, Lausanne, Switzezrland
	Mr Bertand LLORENTE, CRCM, Marseille
	Mr Bertrand PAIN, SBRI, Bron
	Mr Michael SIEWEKE, CIML, Marseille
	Mr Eric SOLARY, IGR, Villejuif
	Ms Madalena TARSOUNAS, University of Oxford, United Kingdom

Scientific delegate representing the AERES:

Mr Daniel OLIVE

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

Ms Anne-Lise Bennaceur-Griscelli (Université Paris-Sud)

Ms Marie-Josephe LEROY ZAMIA (INSERM)

Mr Eric QUÉMÉNEUR (CEA)

1 • Introduction

History and geographical location of the unit

The UMR 967 "Stem cells and radiation" (INSERM, CEA, University of Paris-Diderot/Paris-Sud) was created in January 2009 to investigate the cellular responses of living organisms to environmental or endogenous stresses, with a focus on somatic and germinal stem cells. Geographically, this unit is located within the Institute of Cellular and Molecular Radiobiology (iRCM/DSV/CEA) on the Fontenay-aux-Roses CEA campus. This institute also host other research groups, including the former UMR 217 "Molecular and Cellular Radiobiology" (CNRS, CEA), which terminated in December 2011.

The current project aims at creating a novel Institute of Cellular and Molecular Radiobiology (iRCM) that will result from the fusion between the UMR 967 "Stem cells and radiation" and the UMR 217 "Molecular and Cellular Radiobiology", plus two external teams. It will bring together 12 research groups with a solid expertise in the fields of stem cells and DNA repair. Altogether, the new iRCM will host 78 permanent staff, including 8 professors or assistant professors and 37 researchers.

Management team

The proposed management team consists of a Director (Mr Paul-Henri ROMEO), a Deputy Director (Mr Juan Pablo RADICELLA) and an assistant to the director (Ms Aurélie GOURET). Mr Paul-Henri ROMEO is the current Director of UMR 967. Mr Juan Pablo RADICELLA is a senior PI of the former UMR 217. The Committee has been unanimous to endorse the choice of this management team.

AERES nomenclature : SVE1_LS4

Unit workforce

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	9	7	7
N2: Permanent researchers from Institutions and similar positions	38	39	37
N3: Other permanent staff (without research duties)	18	16	7
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	1	1
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	10	6	4
N6: Other contractual staff (without research duties)	7	6	3
TOTAL N1 to N6	**83**	**75**	**59**

Percentage of producers	***77.63 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	18	
Theses defended	14	
Postdoctoral students having spent at least 12 months in the unit*	14	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	23	

2 • Assessment of the unit

Strengths and opportunities

- Coherent organization and research themes
- Unique expertise in DNA repair and stem cells biology (germinal, hematopoietic, neuronal, skin)
- Strong potential to develop synergies between research projects on DNA repair and stem cells
- Good balance between fundamental and applied research, in line with the missions of CEA
- Overall scientific level is very good, with a large proportion of excellent groups with international visibility
- Successful reorganization of UMR 967, with a significant improvement of the impact of its research
- Very good core facilities and CEA infrastructures
- High success rate to grant applications and European networks
- The unit is attractive to students and postdocs despite its relative geographical isolation
- Good proportion of women among PIs
- Active policy to hire and support junior PIs

Weaknesses and threats

- The proportion of articles published in high impact factor journals needs to be increased
- Relative geographical isolation and complexity of CEA procedures
- The current administrative structure is not sufficient to support 12 research teams

Recommendations

- Create an administrative structure that is adapted to the size of the new unit
- Establish a scientific advisory board
- Implement a mentoring program for junior groups
- Increase the frequency of external seminars to compensate for the geographical isolation of the CEA campus
- Promote exchanges between DNA repair and stem cells groups through the organization of internal seminars
- Increase international visibility of some groups through participation to international conferences

3 • Detailed assessments

Assessment of scientific quality and outputs

The research carried out by iRCM groups can be categorized in the following themes: (i) consequences of cellular stress on the biology of stem cells and (ii) basic mechanisms regulating genetic stability. Overall, this research is of high to very high quality. About one third of the groups are excellent on international standards, the others being considered as good to very good.

The quantity and the quality of the publications are in general very good. Most of the groups have published articles in high impact factor journals such as *Nat Cell Biol*, *J Exp Med*, *Mol Cell*, *Nat Struct Mol Biol*, *Gene Dev*, *Blood*, *PNAS*, *EMBO J*, *PLoS Genet*... The number of outstanding publications has increased over the past five years and this effort needs to be maintained to reach the highest international standards.

Assessment of the unit's academic reputation and appeal

The fusion between UMR 967 and the former UMR 217 will bring together twelve groups with complementary expertise in DNA repair and stem cells biology (germinal, hematopoietic, neuronal and skin). This will undoubtedly increase exchanges between these groups, promote the development of highly synergistic research projects and increase the academic reputation and appeal of the future research unit.

At the individual level, several PIs are senior scientists with internationally-recognized expertise. They are invited to chair sessions at international conferences, participate to European networks and have obtained prestigious prizes and distinctions. Although further effort is needed to establish the reputation of younger PIs, the new iRCM hosts a critical mass of high-profile scientists who will contribute to the reputation and appeal of this new resarch unit.

An important aspect of iRCM appeal is the strong links that it has established with the Universities Paris Diderot and Paris Sud), which contributes to attract PhD students and postdoctoral fellows. This link depends on the presence of 10 professors and assistant-professors within the iRCM teams. This number has significantly decreased over the past years. This represents a major threat for the iRCM and it is essential that this trend is reversed in order to preserve the potential of iRCM to attract young scientistss.

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

The research activity of the iRCM is perfectly line with the missions devoted to the CEA, which are to perform a high-level basic research on radiobiology, with practical implications for medical and societal requests on irradiation and contamination issues. This places iRCM teams in an ideal position to establish strong interactions with their social, economic and cultural environment. This is illustrated by the fact that most of the teams have patents and/or contracts with industrial partners such as EDF, l'Oréal and BASF. Several PIs are also involved in societal debates on bioethics at a very high level (Sénat, Assemblée Nationale). Others contribute to the dissemination of scientific knowledge to a lay audience through interviews and articles in popular science journals.

Assessment of the unit's organisation and life

Most of the teams are used to work together as UMR 967 and groups from the former UMR 217 are currently located in the same building and already share common facilities. This will undoubtedly facilitate the fusion of the two UMR and promote scientific interactions between these groups. Individual teams are generally well managed, with a few exceptions (see evaluation of individual groups).

Governance of the institute by the new management team will benefit from the administrative structures already present in the UMR 967. However, it will be important to strengthen these structures and develop novel management tools to accompany the size increase of the unit. In particular, the committee recommends the creation of a scientific advisory board to help the directors define the long-term evolution of the institute and formalize its recruitment policy. From this respect, the committee praises the iRCM policy to secure the recruitment of promising young PIs by providing them with lab space and a salary while they apply to an ATIP/Avenir grant or to a permanent research position.

Assessment of the unit's involvement in training through research

With 23 qualified research supervisors with an HDR, the iRCM teams are very active in training through research. These teams have trained more than 40 PhD students and postdocs during the review period, with some variability between groups. Several PIs are involved in teaching at different levels (Universities of Paris-Diderot and Paris-Sud). For instance, members of team 1 were involved in the creation and management of the Master 2 "ReproDev" (Paris-Diderot) and in the management of the Master 1 "Cell Biology, Physiology and Pathology". Overall, the unit's involvement in training through research is excellent, but should be improved for some teams.

Assessment of the five-year plan and strategy

Overall, the global aim of this five-year plan is clear and the strategy of the unit is solid and realistic. The fusion of UMR 967 and the former UMR 217 will bring together 12 groups with complementary skills and knowledge on stem cells and DNA repair. Teams 1-6 are expert in germinal, hematopoietic, neuronal and skin stem cells biology. The expertise of teams 7-12 covers different aspects of DNA repair, including base excision repair, homologous recombination, non-homologous end joining and telomere maintenance. Many of these groups are internationally recognized for their expertise on the cellular responses to endogenous and exogenous stress. They have developed original cellular models to investigate these mechanisms, which are also relevant for other teams. Finally, they will share common facilities and CEA infrastructures with the new unit. This is expected to promote collaborations and to create synergies. For instance, collaborations between stem cells (2, 4, 5 and 6) and DNA repair teams (7, 9, 10 and 11) are already planned to investigate stem cells responses to DNA damage and oxidative stress. These collaborations should lead to major breakthroughs in both fields, with important implications for public health. If successful, this strategy will undoubtedly establish the iRCM as a world-leading radiobiology institute.

4 • Team-by-team analysis

Team 1 : Development of the gonads (LGD)

Name of team leader: Mr Gabriel LIVERA

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	5	5	5
N2: Permanent EPST or EPIC researchers and similar positions	0	1	0
N3: Other permanent staff (without research duties)	4	4	4
N4: Other professors (PREM, ECC, etc.)	1	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	0	0
N6: Other contractual staff (without research duties)	1	2	1
TOTAL N1 to N6	**12**	**13**	**11**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	4	4

• Detailed assessments

Assessment of scientific quality and outputs

The LGD team has a history of highly original research within quite a difficult area of study. They have made significant contributions to the field of germ cell meiosis. Very briefly these include novel regulators of meiosis and gametogenesis and critical data on repro-developmental toxicity of certain environmental chemicals and endocrine disruptors on the human foetal gonad in particular. In terms of their scientific impact, the team has a strong publication record within the field. The impact of many of their papers is well above the average in the reproductive development and reproductive toxicity fields. The reputation of some of the journals which have published the team's studies is very good (IF>5, JCEM, EHP, PNAS).

The outlook of the team is good, with participation and/or organisation of national and international meetings and conferences (e.g. European Testis Workshops). This is mirrored by active participation in research networks (e.g. ANTIOPES). The team also participates in international research collaborations as can be seen from their publications.

Assessment of the unit's academic reputation and appeal

This group has an international reputation for important research into the development of the gonad and sex differentiation, endocrine disruption and potentially adverse environmental effects on the development of the human foetal gonad. The field is, in general, a relatively small one but an assessment of the profile of the unit would be in the top 20 % globally. The team has been very active in participation or leadership in international and national projects (e.g. René HABERT leads an ANSES network). The scientific quality has been excellent and other researchers have highly respectable international profiles. Team members participate in Editorial Boards of international journals (e.g. PLoS One) and in a number of important national committees (e.g. ANSES, ANR). They also have participated in a large number of important scientific conferences, including those aimed at bringing clinical and scientific researchers together (e.g. the former PI was a plenary speaker at Fertility 2013 in UK).

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

Opportunities for directly applied research and industrial participation are limited given the research area. However, the team has a contract with EDF. Development of succesful human fetal ovarian xenograft system has considerable scientific and commercial potential and should be expanded. Intellectual property rights should be secured. Beyond that, the team is also active in communicating science and research findings to the public, largely via the press and to schools and government. The latter is an extremely important role. The team has also contributed to industry via organisations such as The European Council for Plasticisers and Intermediates (ECPI). Team members contribute to general science books and magazines which are more accessible to no-specilist scientists and clinicicans as well as the interested public. Communication via the press has been at the national and even international level and includes web, print, radio and televison outlets.

Assessment of the unit's organisation and life

The LGD team must be well organised since it is productive and appears to have the facilities and coordination to maintain an excellent output of novel research findings. However, the retirement of Mr René HABERT is a clear threat and is inevitable at handover from one team leader to another. Mr Gabriel LIVERA has inherited René Habert's contacts and strengths, but at this time the team will need to work even harder to maintain their excellent profile in the field.

Assessment of the unit's involvement in training through research

The team members contribute to a very impressive array of undergraduate, post-graduate, doctoral and post-doctoral teaching and training initiatives, largely in cooperation with a number of national universities. The PhD completion time and rate appears to be excellent. Overall the team has an impressive track-record in research-led teaching and training.

Assessment of the five-year plan and strategy

The proposal to narrow the focus of the team to Germ Cell Meiosis and Endocrine Disruption is excellent, especially since the cross-over and mutual information between the two threads enables them to strengthen and support each other. The one surprise is that there is no mention of direct interaction with team 2 whose work a cognate match, at least for germ cell meiosis (see Minor recommendation below). The focus enables the five-year plan to develop a high level of originality while maintaining a low-risk scenario for the research programme. The appropriate initiation and maintenance of germ cell meiosis is a key developmental limiting factor in establishing adult fecundity and the team's focus on this aspect of reproductive development is competently shared by very few other groups in the world. The second focus on endocrine disruption is also an important area of research although there are a larger number of groups working in the field. However, key factors in the five-year plan, namely the cross-pollination between germ cell meiosis and endocrine disruption research strands and a strong integration of human foetal research in with the animal and *in vitro*/genomic approaches are a clear strength. While not globally unique, there are very few groups who combine first class reproductive development research with endocrine disruption studies, with the use of human foetal material inherent in both.

The five-year plan is not complex and while the different sub-projects are closely inter-linked, they are not necessarily mutually inter-dependent, allowing flexibility. Highly successful progression in any single sub-project will be quite easy to build on and extend. Evidence from the last few years would suggest that the team is very capable of doing so successfully, utilising such opportunities. Continuing collaboration with clinicians at Antoine Beclere Hospital is critical and is highlighted in the strategy document. A new researcher appointment and continuing participation in relevant networks are critical.

Overall the proposed 5-year plan is a focused, highly feasible and allows internal flexibility and cross-pollination. It is very likely that the LGD team will achieve the proposed programme of work within the timeframe outlines.

Conclusion

● Strengths and opportunities:

- Highly relevant research strands with clear opportunities for synergism between research strands

- Clearly defined objectives and pathways to success

- Good publication record within the field

- Program of work builds on existing strengths and facilities, with a good integration of diverse research approaches/techniques

- Development of successful human fetal ovarian xenograft system is unique

- Low risk despite clear examples of scientific innovation

- Funding from various sources to underpin research program

- Good indications of training, educational, social, non-academic and industrial partnerships

● Weaknesses and threats:

- The retirement of René Habert is a threat to the team

- Not enough full-time researchers

- Interaction with Team 2 not transparent or explicitly developed

● Recommendations:

- The recruitment of a new full-time researcher is an important objective

- A good balance between fundamental and more applied research should be maintained

- The team should further strengthen international collaboration and attendance at international conferences

- Development of successful human foetal ovarian xenograft system has considerable scientific (e.g. establishment of the ovarian reserve and biomarkers for problems) and commercial potential and should be expanded. Intellectual property rights should be secured as a matter of urgency, especially with regard to assisted reproductive technologies and advances

Team 2 : Gametogenesis, apoptosis, genotoxicity (LGAG)

Name of team leader: Ms Isabelle ALLEMAND

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1	0	0
N2: Permanent EPST or EPIC researchers and similar positions	4	3	3
N3: Other permanent staff (without research duties)	1	1	1
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	1	0
N6: Other contractual staff (without research duties)	0	0	0
TOTAL N1 to N6	**8**	**5**	**4**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	0	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs

The LGAG team is engaged in a highly competitive field, the characterization of germ stem cells in mammals. Current work focuses on apoptotic pathways in spermatogonia under normal or stress conditions, using mouse as a model organism. The approaches developed by this group reveal the potential and plasticity of some germ cells and their progenitors, both *in vitro* and *in vivo*. The contributions of the LGAG group are very important, as illustrated by the high impact of its proper publications (*Nat Cell Biol*, *Stem Cells*, *Hum Mol Genet*). This is remarkable considering the small size of this team. The publication record as senior author of the new group leader is rather weak, but two manuscripts are in preparation.

Major achievements concern (*i*) the role of DNA repair pathways, especially Fanconi Anemia, in the maintenance of the stem cell pools of different tissue (*ii*) the involvement of both intrinsic (mitochondrial apoptotic Puma) and extrinsic (death receptor Trail/Dr5) pathways in depletion of spermatogonia pool after irradiation, and (*iii*) the demonstration of male germ cells plasticity (late c-Kit transit amplifying progenitors) with the ability to reprogram their fate by de-differentiating in functional germ stem cells. This last publication is outstanding and of major importance in the field.

Assessment of the unit's academic reputation and appeal

Despite its small size, the LGAG appears to be active in collaboration at both national and international levels. In particular, ANR projects were granted allowing the development of the human force. The former PI (and to a lesser extent the new PI) is frequently invited to speak at international conferences. The *Nat Cell Biol* publication was selected for a platform presentation at the French Academy of Sciences. Team members are involved in peer reviewing for international journals, funding agencies (ANR) and biomedical agencies.

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

Although the involvement of the team with the social, economic and cultural environment is difficult to assess, one publication in a general scientific French journal (Médecine Science) can be seen as an effort to diffuse knowledge to the public. An important industrial partnership with EDF is also mentioned, but the nature of this partnership is not detailed.

Assessment of the unit's organisation and life

The LGAG team is involved in multiple collaborations with other teams within or outside of the unit, which led to high-level publications. However, scientific interactions with Team 1 should be increased. Another organizational concern is that the senior author of most recent publications of the LGAG is not the group leader.

Assessment of the unit's involvement in training through research

The team hosted only a few graduate and undergraduate students during the evaluation period. The brilliant achievement of a PhD student attested by leading publications in 2008 and 2009 should attract new students in the future. The team also hosted two post-doctoral fellows during the review period, but only one is currently present.

Assessment of the five-year plan and strategy

The five-year plan is in line with the previous achievements of the LGAG and builds on the strengths and expertise of this team. The proposal focuses on the role of apoptosis in the maintenance of germinal stem cells and on the consequences of irradiation. The team was restructured to anticipate this evaluation and Isabelle Allemand took the lead in 2009. The involvement of the former group leader was beneficial for the global production of the group. Both PI beneficiate of contacts and collaborations that will synergize the group and the projects in the future.

The three main research axes concern i) the impact and role of Fanconi Anemia genes on germ cells development and differentiation, ii) the plasticity of the Germ cells with the germinal reprogramming and iii) the identification and characterization of factors involved in the maintenance of the germ stem cell niche. These goals are well described and the experimental proposed plans demonstrate that some of them are already actively engaged.

However, few points should probably be presented more in details including a more precise schedule of the research outputs (axes 2 and 3), the identification of specific new transgenic models (axis 3), the management of all mutant mice (axis 3), even if some will be shared through collaborations. One of the key questions remains the limited size of the team to achieve all the proposed goals.

Conclusion

● Strengths and opportunities:

- High-quality focused research

- Good recognition of team member's achievements in the germ stem cells field

- Good publication record, with a significant proportion of high and very high impact publications

- Well-balanced five-year plan, combining risk-taking and more feasible research strands. Clear strategy and good synergy between research strands

- Good academic networking, seems to be a development of external collaboration briefly mentioned

- Good funding stream available

● Weaknesses and threats:

- Small size of the team, with few students/postdocs

- Lack of international networking

- Past and current academic grants were mostly obtained by the previous group leader

- The current team leader is senior author of only one of the main publications of the group

● Recommendations:

- Work more closely with team 1 and develop external collaborations to increase the impact of the LGAG research and compensate for the small size of the group

- Efforts should be made to hire new students and postdocs

- Increase participation to international meetings and international networks

- Restrict the number of mice models to be developed

- The new group leader should author more articles as senior author to secure funding

Team 3 :

Molecular Pathways implicated in the expansion and transformation of human hematopoietic stem and progenitor cells (LSHL)

Name of team leader:

Ms Francoise PFLUMIO

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1	2	1
N2: Permanent EPST or EPIC researchers and similar positions	2	2	2
N3: Other permanent staff (without research duties)	2	1	1
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	0	0
N6: Other contractual staff (without research duties)	0	2	2
TOTAL N1 to N6	**6**	**7**	**6**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

The PI has produced lead author publications of high standard ranging from the best journal in the specialty (Blood, Leukemia) to journals with general cross-discipline impact (JEM). With a moderate size team she has produced at least one original paper in a high-ranked journal each year (Stem cells and Blood in 2008, Blood in 2009, Leukemia in 2010, J Exp Med and Leukemia in 2011). In addition, the team has been interacting with other excellent groups, which led to papers in Blood (2), Stem Cells (3), J Exp Med (3), Cell (1), Nature Medicine (1), Hum Mol Genetic (1), Haematologica (1), and PlOS one (1). Excellent level. She has made important contributions to the understanding of the general molecular mechanisms that control human stem cell self renewal and maintainance. Her work on T-ALL also lead to findings with significant implications for diagnosis and therapy of this disease.

Two aspects in the group research program deal with SCL/TAL1 transcription factor. The team explored:

1) its fine tuning in hematopoietic stem cell development, at levels tightly defined. Two targets are especially studied: DDiT4/REDD1 that encodes an mTOR inhibitor and CCL2 that attracts macrophages in the niche.

2) its role in the molecular mechanisms of T-ALL, i.e. the functions of the transcription factor NKX3.1 in TAL1-mediated leukemogenesis.

In addition, in T-ALL, the teams examined the interactions of leukemic and stromal cells, the role of microRNA, that of Notch, the cellular and molecular heterogeneity of the disease, and its evolution with progression.

Exploration of both normal and leukemic hematopoiesis provided exciting and complementary information. The work done was coherent, and technical approaches (combination of *in vitro* and *in vivo* models, including primary cells injected in immunocompromised mice) were appropriate and ambitious.

Altogether, the LSHL team has performed high-quality research during the review period, leading to good to excellent publications and significative improvement of knowledge.

Assessment of the unit's academic reputation and appeal

The team leader is invited to international conferences and lectures. She has organized and participated in national and international workshops and participated in national networks. Her work has been honored by prize from the Société Française d'Hématologie.

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

The team leader communicates with the academic community outside of the natural sciences (philosophical sciences) and the general public (press release, university outreach interview) and contributes as an expert to a foundation promoting women in science.

Assessment of the unit's organisation and life

A small team with a clear leadership and a progressive extension. The number of researchers or teacher-researchers increased from two to four during the review period.

Assessment of the unit's involvement in training through research

The team has trained two PhD students who successfully defended their thesis during the review period. Three other PhD students are currently working in the team. The team has also provided training opportunities to younger students.

Assessment of the five-year plan and strategy

The proposed projects are in line with the line of the previous work.

- In normal hematopoiesis, the team will pursue the exploration of TAL1 functions, with the hypothesis that a feedback loop between hypoxia and TAL1 through mTOR delineates HSC fate, which is an excellent question, given hypoxia in BM niches. The hypothesis is supported by data from gene array expression analysis in human HSC with a shRNA KD of TAL1 that show increased expression of Ddit4/REDD1 a negative regulator of the mTor pathway and up-regulation of Hif1alpha, a key transcription factor in hypoxia mediated HSC quiescence. The team proposes to use inducible shRNA and overexpression systems or chemical inhibition of components of the investigated signalling cascade to determine the functional interaction of the studied components.

Using similar approaches the team also plans to explore another regulatory loop between TAL1 and GATA-3 and/or GATA-2 and its effect on HSC proliferation and differentiation.

- In T-ALL, the team will also further explore the TAL-1/GATA-3 connection by identifying common pathways between TAL1 and GATA 3 in HSC and T-ALL cells to identify regulators that activate stem cell properties in leukemic blast and study their importance for leukemia initiation and propagation.In addition, the respective characteristics and properties of CD34+ and CD34- leukemic cells will be explored, together with the mechanisms of central nervous system infiltration analyzed in a mouse model, interaction with stromal cells (based on the surprising and exciting observation that T-ALL cells modulate the growth of MS5 cells), and the role of microRNAs in TLX3 induced T-ALL.

These projects are coherent, based on interesting and well founded hypotheses that are for most parts supported by preliminary data. They are also well aligned with the expertise of the team and the technological tools available. The expected results are of significant interest both for fundamental research and clinical science. The team leader plans to use modern techniques and to apply emerging concepts to her own field of interest by developing meaningful collaborations with relevant experts. The developed projects are complementary and for most parts well integrated into the overall research topic of the team.

Compared to previous work, the team obviously aims at focusing on specific aspects of the program while still working on both normal and pathological hematopoiesis in a complementary fruiful manner, mixing basic and translational research, *in vitro* and *in vivo* models. The strategy that will be used to validate (or eliminate) their exciting hypotheses are basically those that have been used by the team in the recent years with much efficacy.

The only concern of the committee is that for a relatively small team (6-7 people) perhaps too many lines of research are being developed, especially as some of them reach out into diverse new competive research areas and complex techniques (miRNA, ChIP-seq, MSC).

Conclusion

● Strengths and opportunities:

- Excellent research activity, assessed by a very good track record

- Hypothesis-driven research with clear aims and focused objectives

- Ambitious approaches combining *in vitro* / *in vivo* and basic / translational aspects

- The team leader is firmly established expert in human hematopoietic stem cell biology and T-ALL leukemia.

- She is well integrated the national hematopoiesis community and established meaningful collaborations at the institute level, regionally and nationally to apply modern concepts and techniques to her own research questions and areas of expertise.

- During the review period she has shown a very good productivity for a moderately sized team and also attained international visibility with interesting recent results

● Weaknesses and threats:

- The team may be too small to cover all new projects at a competitive level

- Recommendations:

- A focus on fewer of the projects that venture into new domains would probably help the group to have a higher impact on the selected studies. Alternatively, the PI should recruit new researchers in the next years.

Team 4 : Neural stem cells and radiation (LCNNC)

Name of team leader: Mr François BOUSSIN

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	0	0	0
N2: Permanent EPST or EPIC researchers and similar positions	6	6	6
N3: Other permanent staff (without research duties)	1	1	1
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1	0
N6: Other contractual staff (without research duties)	0	0	0
TOTAL N1 to N6	**8**	**8**	**7**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs

The team of Mr BOUSSIN is very active, with six researchers investigating the radiobiology of neural stem cells (NSC) and glioma stem cells (GSC). This group has made significant contributions to the field of neuronal stem cell activation, growth and responses to ionizing radiation, including 12 publications in good journals (EMBO J, Nucleic Acids Res, Stem Cells, Cell Mol Life Sci), a patent and 11 other publications as collaborations. In addition, work in the lab is focused on telomere maintenance and has shown that about 30% of human gliomas rely on pathways of telomere elongation alternative to telomerase (alternative lengthening of telomeres, ALT).

Current research topics include mechanisms of DNA repair in NSC progenitors when irradiated at low dose rates, crosstalk between DDR and cell fate control in irradiated NSP cells, mechanisms of resistance to radiation by TGFa in neural progenitor of pallial-subopallial boundary, radiation-induced migration of NSPC and glioma stem cells, involvement of ALT mechanisms for maintenance of its telomeres in glioma stem cells and effect of tritium contamination on NSP cells.

Assessment of the unit's academic reputation and appeal

The group leader is actively involved in meaningful collaborations and jointly funded projects, both at national (ANR, INCa) and international levels (FP7, Ecos).

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

The activity of this team is well linked to its social, economic and cultural environment, as illustrated with contracts with industrial partners such as EDF and CEA-IRSN, with the dissemination of scientific knowledge (article in Atouts Bio, participation to the “Mission Patrimoine 92”) and with the implication of one of the team members in a national association of PhD students.

Assessment of the unit's organisation and life

No information provided on this aspect. It should be noticed that the number of staff scientist in this group has significantly decreased since 2009.

Assessment of the unit's involvement in training through research

The LCNNC is an excellent environment for graduate student training, with three PhD students currently working in the lab and five defended PhD dissertations in the past quinquennium. The PI is involved in the jury of Master 2 “Biologie du vieillissement” and in the jury of Ecole doctorale GC2ID (2012). One of the staff scientists (C Granotier) completed her PhD in 2008 in this lab.

Assessment of the five-year plan and strategy

The proposal presents a comprehensive list of *in vivo* and *in vitro* approaches to address key questions in neural stem cell and progenitor cell responses to low-dose ionizing radiation, as well as the impact of ionizing radiation on neuronal cell fate control during embryonic development. This is particularly relevant to the clinic, as exposure to radiation during fetal development is known to have deleterious consequences for nervous system structure and intellectual performance later on in life. An important aspect of the proposal is focused on the contribution of ALT to radiation resistance in neural stem cells. All the above lines of research have strong clinical applications both in prevention of neurological diseases and glioma cell therapies.

If all the proposed projects are very interesting, they are not always linked together and this diversity may represent a threat in the long run. Moreover, it is not clear who and how many people are involved in each research axes.

Conclusion

● Strengths and opportunities:

- Well-established laboratory that has made significant contributions to the field of neuronal stem cell activation, growth and responses to ionizing radiation

- The LCNNC is well funded, with an European contract (oct 2012), several grants from ANR, ARC and EDF

● Weaknesses and threats:

- The group has a very good, but not outstanding publication record, given its size

- If all the proposed projects are very interesting, their multiplicity and diversity could represent a serious threat for the team

- The experimental approaches used to assess the contribution of ALT to the DNA damage response in irradiated gliomas will be carried out in a single glioma cell line. One wonders about the physiological relevance of these results, unless other cell lines or model systems are used.

● Recommendations:

- The proposed five-year plan would benefit from the establishment of additional cellular models for glioma to address the response to ionizing radiation and telomere de-regulation. These cell-based approaches should be complemented with *in vivo* mouse studies and analysis of clinical samples for known ALT signatures.

- The team should focus on radiation-induced mechanisms of damage, repair or resistance on normal neural stem cells models

- The number of researchers with HDR should be increased

Team 5 : Repair and transcription in stem cells (LRTS)

Name of team leader: Mr Paul-Henri ROMEO

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1	1	1
N2: Permanent EPST or EPIC researchers and similar positions	7	7	7
N3: Other permanent staff (without research duties)	0	0	0
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	1	1
N6: Other contractual staff (without research duties)	2	1	0
TOTAL N1 to N6	**12**	**10**	**9**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
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	0	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

The team headed by Mr Paul-Henri ROMEO explores adult hematopoietic stem cells, either healthy or transformed. The performed research included basic aspects such as molecular biology of transcription regulation, and translational aspects dealing with the mobilization of stem cells and their response to tritium irradiation. In addition, the team has explored (metabolomics) or developed (imaging) new research tools that improve our understanding of diseases (metabolome of red cells) and bone marrow reconstitution (imaging). This conducted research, totally focused on the hematopoietic tissue, mostly stem cells, used a variety of approaches and the main results can be summarized as follows:

1 – The team identified TIF1γ as a regulator of transcription (TAL1 and PU1 interactor) during adult hematopoiesis, using modeling in mice (Cell Stem Cell)

2 – In the context of acute T cell lymphoblastic leukemia, the team has shown that the oncogenic effect of the transcription factor TAL1 is mediated in part by the activation of the gene NKX3.1 and identified its recruitment in a TAL1/LMO2/Ldb1/GATA3 complex (J Exp Med)

3 – Long-term exposure of murine HSC to tritium compromises the HSC capability to reconstitute hematopoiesis by affecting its proliferation rate (Int J Rad Biol)

4 – Synthetic oligosaccharides that mimic heparan sulfate could be used in combination with G-CSF and CXCR4 inhibitor to mobilize stem cells for transplantation (Haematologica)

5 – A fiber optic probe can be introduced in the femoral cavity of living mice to follow hematopoietic reconstitution by fluorescent cells, which paves the way for multiple applications (Blood, Haematologica)

6 – The metabolomic signature of altered red cells in genetic diseases such as sickle cell disease, thalassemia or stomatocytosis could be used to further explore the pathophysiology of these diseases (Blood, Haematologica).

The LRTS published 13 articles in which PH Romeo is the last author between 2007 and 2012, including two reviews and excellent papers in Cell Stem Cell, J Exp Med, Blood (including a plenary paper) and Haematologica, covering the diverse aspects of the project, with a very high international visibility. The LRTS also published 14 articles in collaboration with other teams, including papers in PLoS Biology, Stem Cells, Blood, Diabetes, Circulation Res, Dev Biol, Leukemia, J Biol Chem and Development. Some of the papers of researchers of the team are not listed (e.g. N Gault D Lewandovski, Blood 2012).

Altogether, the LRTS has achieved the creative integration of hypothesis-driven research projects, using original approaches and up-to-date techniques. This group has applied the strength of available CEA technology to address questions of fundamental and clinical interest, bridging fundamental and translational research. This resulted in high-quality results, excellent publications and clear improvement of knowledge and tools (two patents).

Assessment of the unit's academic reputation and appeal

The team leader has received the Rosen Prize award in 2008. He is member of the Tohoku Medical Society (Japan). His post-doctoral student who worked on TIF1γ and NKX3.1 received two prizes from the Société Française d'Hématologie.

The team leader assumes important tasks in the management of the French research landscape, principally as the head of the ITMO Immunology, Hematology and Pneumology of Avisan. Despite this undoubtedly time consuming task, the team appears to continue on an upward trajectory regarding networks and scientific developments.

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

The unit plays an essential role in the Biological deparment of the CEA. Two synthesis in Med Sci in the last years. One of the research subject was done in collaboration with a company, Endotis Pharma (two patents).

Assessment of the unit's organisation and life

The high productivity of the team is associated with a high turnover of researchers. Several have left the team during the past three years, but one or two new researchers are recruited each year.

Assessment of the unit's involvement in training through research

The LRTS currently hosts one PhD student and three post-doctoral fellows. No indication on undergraduate students recruitment and formation. Training through research should be improved by hiring more students, which should not be difficult considering the attractivity of this group.

Assessment of the five-year plan and strategy

The proposed project is based on these previous results and is well focused, concentrating on the most promising developments and integrating previous lines of research into one direction. The proposal is based on important questions, well founded hypotheses and solid preliminary data. It uses modern, up to date technology (ChIP-Seq, mouse genetic tools) and assembles experts or initiated collaborations to perform these tasks at a qualitatively high level.

Several of the previous programs will be stopped, including the mobilization of stem cells by heparan sulfate (Pharma has stopped producing the tested HS), and the tritium effects on HSC. The project is focused on TIF1γ on one hand, and low doses irradiations on the other. Preliminary observations made with the Tif1γ model (2 researchers, 2 post-docs) are especially exciting with a role of the protein in regulating the inflammatory response. The exploration is made in mice with up-to-date approaches and appropriate collaborations, and may provide a new angle to explore, and possibly treat, the inflammatory response. Regarding radiations (3 researchers, 1 PhD student), the team will focus on chronic irradiation with low doses inducing radical oxygen species to alter hematopoietic stem cell functions and the molecular mechanisms of these effects will be explored using various mouse models.

Conclusion

● Strengths and opportunities:

- Excellent hypothesis driven science, well focused on hematopoietic stem cell, with excellent publications

- Diversity of approaches, development of tools

- Excellent collaborations and network of interactions

- Stable, well funded team

● Weaknesses and threats:

- Low production of CEA researchers and low number of PhD students and post-doctoral fellows

● Recommendations:

- Stimulate, when possible, the scientific contribution of CEA researchers

- Try to connect to clinics (inflammatory diseases)

Team 6 : Keratinocyte stem cells, regenerative potential and genomic stability (LGRK)

Name of team leader: Ms Michèle MARTIN

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions		0	
N2: Permanent EPST or EPIC researchers and similar positions		4	3
N3: Other permanent staff (without research duties)		3	
N4: Other professors (PREM, ECC, etc.)		0	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		0	
N6: Other contractual staff (without research duties)		0	
TOTAL N1 to N6		**7**	**3**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students		0
Theses defended		6
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		3

• Detailed assessments

Assessment of scientific quality and outputs

The team of Ms Michèle MARTIN has produced original data showing that keratinocytes stem cells (KSC) have a high capacity to repair DNA damage and that FGF2 signaling is involved in this process. These results have been published in Stem Cell in 2010. They have shown the role of TGF beta signaling in the stemness maintenance and identified two candidate transcription factors implicated in the circuitry of TGF beta. They have begun to explore the function of Klf4 and analysis of the role of Mad4 is ongoing.

The LGRK has also set up a new method to study KSC that is of crucial importance for their future project. A particular strength of the group is the close collaboration with clinical teams to develop new cellular models from patients suffering from the Gorlin's syndrome. They also collaborate with different research groups and platforms for high throughput analysis of the different models. The *in vivo* model of reconstituted skin grafted in nude mice is also a powerful tool for the achievement of their projects.

Quality and quantity of publications is in the good range. The team of Ms Michèle MARTIN published 15 articles during the review period. Ten were primary articles from the group and the other five were obtained from collaborative studies. Apart from one article in Stem Cells (IF 8.6), most of the articles were published in journals with and IF around 5 or below.

Assessment of the unit's academic reputation and appeal

The PI is well recognized in her domain and participates to many scientific councils in France. Ms Michèle MARTIN and to al lesser extent other scientists were invited to 16 international meetings during the review period, which is quite significant. The team participates to European collaborative networks RISK-IR and Euratom. Ms Michèle MARTIN is member of the task group "Stem cells and radiation carcinogenesis" at the IRCP. The international reputation of the LGRK could be further improved by increasing the impact of the journal this group publishes in.

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

The team has several contracts and patents with industry (EDF, L'Oreal, BASF) and is involved in social debates on bioethics at a very high level (Sénat, Assemblée Nationale, Universities). The PI is also very active in communicating Science to the public through multiple articles in journals such as Ca m'interesse, Sciences et Avenir, l'Express…

Assessment of the unit's organisation and life

The LGRK team is located on another campus, fairly distant from the iRCM. In the long run, this represents a serious threat for the ability of this team to maintain interactions with the rest of the unit.

Assessment of the unit's involvement in training through research

Altogether, the team hosted six master students, six PhD students and two postdocs during the review period. M. MARTIN and N. FORTUNEL are involved in several courses on stem cell biology, radiobiology and cancerology of the Universities of Paris V, VII and XI.

Assessment of the five-year plan and strategy

The five-year plan relies on strong data obtained previously by the group. The international competition on these topics is high but the expertise of the LGRK is solid and the hypotheses to be tested are original. The research staff is adequate (two technicians and one engineer for three full-time researchers). However, recruitment of junior researchers (students and postdocs) is important for the future of the team.

The first part of the research program concerns TGF beta and the molecular determinants of the stemness and self-renewal of human KSC. This part of the project is well designed and relies on a scientific strategy that is well mastered by the group. One of the main issues is to identify relevant genes among all those that are involved in

stemness. A more integrated study, positioning the transcription factor selected by the team, should be envisaged to increase the relevance of this analysis.

The second part of the project aims at exploring the effect of ionizing radiation on KSC. This is important to understand the physiopathology of carcinogenesis and to understand the role of low dose radiation in different settings. This project is based on a solid expertise in the field and extends the result on different populations of keratinocytes of stem or progenitor cells. The experimental models are original. The scientific strategy is classical and mainly involves phenotypic analysis.

In a second approach, the team will focus on the Patched1 SHH Gli pathway. The use of cell coming from Gorlin's syndrome patients is original and must be exploited to decipher the role of the SHH pathway. This topic is very interesting and also highly competitive.

Overall, the project is sound and well described, including the researchers and technicians involved in each task. It addresses important questions on the pathways involved in the stemness of keratinocytes stem cells, as well as the role of the studied targets on the functions of these cells, using *in vitro* and *in vivo* models. The project aims also at understanding the radiosensitivity or resistance of KSC and the mechanisms involved in this regulation. It also addresses important questions that are relevant to specific clinical situations.

Conclusion

● Strengths and opportunities:

- Solid five-year plan, relying on the expertise of the team

- Well-funded team (DGA, OSEO, EURATOM, RISK-IR, ANSES), several contracts with industry (l'Oreal, BASF)

- The team is actively involved in formation by research

- High international visibility, the PI and researchers are regularly invited to international meetings

- Strong interactions with socio-economic environment and implication in social debates on bioethics

- Strong communication with the press (Reader's Digest, L'Express, RTL…)

● Weaknesses and threats:

- Not enough articles in high-impact journals

- Location of the group on a distant campus

● Recommendations:

- Aim for higher impact journals

- Join the main CEA campus to facilitate collaborations with other iRCM teams

Team 7 : Genetic instability (LRIG)

Name of team leader: Mr Pablo RADICELLA

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions		0	
N2: Permanent EPST or EPIC researchers and similar positions		5	5
N3: Other permanent staff (without research duties)		1	
N4: Other professors (PREM, ECC, etc.)		0	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		0	
N6: Other contractual staff (without research duties)		0	
TOTAL N1 to N6		**6**	**5**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		4

• Detailed assessments

Assessment of scientific quality and outputs

The LRIG team investigates the molecular mechanisms of DNA repair in mammalian cells, with a focus on base excision repair (BER) and the response to oxidative stress. Another important line of research in the Radicella lab concerns the mechanisms of genetic variability of the human pathogen *H. Pylori*. Mr Pablo RADICELLA is well known at the national and international levels for his numerous contributions to these fields of research.

One of the most important results obtained during the review period concern the characterization of "repair centers" associated with open chromatin and the relocalization of the BER machinery to these speckles in response to oxidative stress. Interestingly, they also found that the BER protein Ogg1 is sensitive to oxidation and that particularly sensitive alleles are associated with cancer predisposition. Finally, the group reported that Pol1 from *H. pylori* has an unexpected role in translesion DNA synthesis and is involved in the genetic variability of this pathogen.

This activity resulted in 9 peer-reviewed articles, most of which were published in good to very good journals (2 PLoS Genetics, Nucleic Acids Res, J Cell Sci, Cancer Research) and 10 articles resulting from collaborations.

Assessment of the unit's academic reputation and appeal

During the review period, the PI was invited to give 22 seminars or lectures at international conferences, which reflects his excellent international reputation. This group is involved in various national and international collaborations. In particular, Mr Pablo RADICELLA coordinates two collaborative projects funded by ANR and is involved in multiple bilateral collaborations funded by the Foreign Affair Ministry with groups in Argentina, Brazil, Germany and Italy. The members of the group also regularly give oral presentations and posters at international meetings. Finally, it is worth noting that Mr Pablo RADICELLA is also the Deputy Director of the iRCM, which represent a very important duty, considering the size of this institute.

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

Work in the LRIG focuses on important scientific issues that also have major implications for public health. These include the mechanisms of genetic variability of the human pathogen *H. Pylori*, which colonizes 50% of the human population and has been implicated in cancer development. Work on BER mechanisms is also highly relevant for radiobiology and LRIG is funded by EDF to study the effect of radiation on biological systems.

Assessment of the unit's organisation and life

The LRIG is organized in two subgroups working on BER in mammals and genetic variability in *H. pylori*. Overall, the structure of the lab is stable, with one staff scientist joining the lab in 2012. There is also a good turnover of postdoc and PhD students.

Assessment of the unit's involvement in training through research

The LRIG is very active in training through research, with five PhD students and two master students trained during the review period. The PI is involved in many Master courses and PhD/HDR committees.

Assessment of the five-year plan and strategy

The five-year plan is clear and well-focused. It builds on earlier work from the LRIG team and will extend the two research area for which the group is already well known, namely BER mechanisms and genetic diversity in *H. pylori*. Projects on BER will follow up on the subnuclear organization of repair foci. A particularly exciting line of research concerns the potential role of the prion protein in the regulation of BER activity. If this connection is confirmed, it will certainly lead to a publication in a very high impact journal.

Work on the genetic diversity of *H. pylori* will explore different mechanisms underlying the genomic plasticity of this organism, such as translesion DNA synthesis, homologous recombination and horizontal genetic transfer. *H. pylori* colonizes approximately half of the human population. Understanding how genetic diversity arises in this organisms and how it helps escape treatment is therefore a major challenge for public health.

Overall, the feasibility of the project is excellent and the expected results will have important implications for both fundamental research and public health.

Conclusion

● Strengths and opportunities:

- The team leader has a strong reputation in both research fields covered by the LRIG

- The five-year research plan is original and should yield important discoveries, including an unexpected link between the prion protein and BER

- With five permanent researchers, one technician and at least two PhD students, the LRIG has a critical mass to fulfill two main projects on two different model systems

- The LRIG takes advantage of the CEA scientific resources to set up original approaches and to address important questions with major implications for public health

● Weaknesses and threats:

- The broad spectrum of the project will require a good supervising to be finalized

● Recommendations:

- Overall, the LRIG team is well established and regularly publishes on the two main topics developed in the lab, although these topics involve completely different model systems. The major recommendation would be to keep going this way, paying a special attention to the project supervision given the broad spectrum of the themes covered.

Team 8 : Genetic and molecular radiobiology (LRGM)

Name of team leader: Mr Xavier VEAUTE

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions		0	
N2: Permanent EPST or EPIC researchers and similar positions		4	4
N3: Other permanent staff (without research duties)		1	
N4: Other professors (PREM, ECC, etc.)		0	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		0	
N6: Other contractual staff (without research duties)		0	
TOTAL N1 to N6		**5**	**4**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		1

• Detailed assessments

Assessment of scientific quality and outputs

The LRGM was created two years ago. It is therefore difficult to assess its scientific output as a team. Yet, it is composed of three researchers with solid publication records. Mr Xavier VEAUTE, the team leader, was first author of a key Nature paper in 2003, unraveling the anti-recombination function of Srs2. Mr Xavier VEAUTE followed on the characterization of Srs2 and continued to publish in high-profile journals since then. During the review period, Mr Xavier VEAUTE was senior author of two articles in *Molecular Cell* and *Nucleic Acids Research*. He is also co-author of a Nature paper, in collaboration with a UC Davis team. Another scientist brings his expertise on DNA polymerase delta to the lab. He is first or last author of two articles in *DNA Repair* and *Mol Cell Biol* and co-author of a *PLoS Genetics* with a Milan team. Another scientist yet has published three articles on homologous recombination with a team in Brandeis University, MA in *Genetics* and *PLoS Genetics*, two of them as first author.

Assessment of the unit's academic reputation and appeal

The LRGM could be viewed as the follow up of a previous team, who was internationally renowned for his seminal work on DNA recombination and repair. This team has been extensively reorganized and was re-created in its present form only two years ago. It is therefore too early to assess the academic appeal of the team. Individually, the LRGM team members are well known in their field. They are regularly invited for seminars or platform presentations at national and international conferences. The team leader is also involved in the organization of national conferences. He is a reference in the field of DNA translocase/helicase and serves as reviewer (Mol Cell, PLoS Biol, Mol Cell Biol) and as expert on several committees (member of the scientific committee of ARC, reviewer for ANR, member of PhD and HDR committees).

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

The mission of the LRGM is essentially to increase the scientific knowledge on fundamental biological processes involved in the maintenance of genetic integrity. By regularly publishing its scientific results, the LRGM fulfills most of its social, economic and cultural missions.

Assessment of the unit's organisation and life

The core of the LRGM is currently based on three senior researchers of comparable age and experience. Although they have collegially chosen Mr Xavier VEAUTE to lead the group, leadership issues could arise, which represents a major threat considering the past history of this group. It is therefore important that VEAUTE rapidly establishes himself as the leader of the group, with the support of the directors of iRCM.

Assessment of the unit's involvement in training through research

The LRGM currently hosts only one PhD student. With three permanent researchers, this team should be more active in scientific training and should be able to attract more PhD students and postdocs in the future.

Assessment of the five-year plan and strategy

The research plan builds on current skills and expertise of the team members to increase our knowledge in the control of homologous recombination, both in yeast and in human cells. The proposed yeast genetic and biochemical approaches are well mastered by the team and should lead to important advances in the field. The search for functional homologues of the yeast Srs2 helicase in human cells relies on collaboration with team 12 and a team at Curie-Orsay. Although this part of the project is very risky and may prove unsuccessful, it will benefit from the use of an original screening approach developed by Gazin and from the unique expertise of the LRGM in recombinational DNA repair.

Conclusion

● Strengths and opportunities:

- The LRGM brings together three senior researchers with excellent skills in genetics and biochemistry and with a renowned expertise in the field of homologous recombination

- Researchers have established fruitful collaborations with international leaders in the field.

- The team has the critical mass and the expertise to make major breakthroughs in the field and to become a leading group in the future unit

● Weaknesses and threats:

- The presence of three senior researchers may favor leadership issues

- The team hosts only one PhD student and no undergraduate student or postdocs. This could represent a threat for the dynamics of a team

● Recommendations:

- The iRCM directors should help the PI strengthen his leadership within the team

- The publication of recent advances on Srs2 and Rad52 should be seen as a priority

- The team needs to attract new PhD and under-graduate students

- The team should expand its field of investigation to less competitive area. The proposed Rad52 interactome studies and the RNAi screen may be instrumental for such a diversification

Team 9 : Repair and ageing (LREV)

Name of team leader: Ms Pascale BERTRAND

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions		0	
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.)		0	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		0	
N6: Other contractual staff (without research duties)		0	
TOTAL N1 to N6		**4**	**3**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		2

• Detailed assessments

Assessment of scientific quality and outputs

The LREV team has been created in late 2011. The current PI emerged from and took the lead of a group initially directed by Mr Bernard LOPEZ, a renowned leader in the DNA repair field.

Since the publication record concerns mostly the period before the creation of the team, it is too early to make a statement on the scientific production of the LREV in its present form. Nonetheless, the publication record of Ms Pascale BERTRAND is very good considering the size of the team. Important contributions have been published together with Mr Bernard LOPEZ. In particular, Ms Pascale BERTRAND is co-corresponding author of two important publications in *PNAS* and *Nat Struct Mol Biol*. Moreover, she is senior author of a publication in *EMBO J* in 2012. Remarkably, all three articles were highlighted in these journals. The EMBO J article is relevant to one of the main projects of the group, which is an excellent start.

The PI has a wide expertise in the DNA repair field. The presence of a junior scientist with complementary skills is an important asset for this emerging group. Altogether, the group is composed of six people, including four staff scientists (three researchers and one technician), one PhD student and one postdoctoral fellow.

Research in the LREV laboratory focuses on important questions regarding the role of the nuclear architecture protein Lamin B1 in the control of DNA repair and genome/telomere stability in physiological and pathological aged-related situation involving ROS production.

Assessment of the unit's academic reputation and appeal

The PI is a promising group leader, who succeeded in establishing a viable research team after the departure of the former PI. She is regularly invited to present her data at national conferences, but still needs to increase her visibility at the international level. Ms Pascale BERTRAND acts reviewer for international journals and for national funding agencies. She has established critical collaborations in France and abroad.

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

The PI contributed to the publication of articles for the external journal of CEA and for the journal of the donators of the « Ligue contre la Cancer ».

Assessment of the unit's organisation and life

The LREV is a well-organized group, mostly composed of scientists who are used to work together. The transition from the former to the new PI went very smoothly and is apparently a success.

Assessment of the unit's involvement in training through research

The LREV is very actiively involved in training through research. Several members of the group participate in the mentoring of M1, M2 and PhD students. The PI was involved in ten PhD or HDR committees.

Assessment of the five-year plan and strategy

The major part of the five-year plan addresses the role of lamin B1 in genome stability. This is an important and timely question because increased levels of lamin B1 are found in ataxia telangiectasia (A-T) patients. Elevated lamin B1 expression was recently shown by the group of Ms Pasacle BERTRAND (in collaboration) to be mediated by oxidative stress and to lead to nuclear shape alterations that impact on gene expression and on the DNA damage response.

The current proposal is a comprehensive and logical plan on how to further investigate the mechanisms of lamin B1 accumulation and its consequence for DNA repair and p38-mediated senescence. The research proposal is very dense and contains several open-ended questions. For instance, it is unclear how the project will benefit from a mouse model of lamin B1 overexpression. Is this mouse likely to be viable? If viable, how will the DNA damage response be assessed at organismal level? Nethertheless, it is clear that the LREV has already made key contributions to the understanding of the role of lamin B1 in DNA repair (published and unpublished data) and these will represent a solid basis for future studies.

The second part of the research proposal is focused on atypical A-T patients, which may lead to the identification of novel separation-of-function mutants in the human ATM gene. This is an interesting concept and may enable advance in our understanding of the disease causes and progression.

Overall, the five-year plan is solid and should lead to major advances in the field, in line with earlier work from this group.

Conclusion

● Strengths and opportunities:

- The PI was successful in establishing a viable group after the departure of B. Lopez and in attracting new staff scientists, which is critical for the future of the team

- The group leader has a strong expertise in the field of DNA repair and has already published important contributions on the subject

- The PI found a research niche with the analysis of the role of lamin B1 in DNA repair and genome stability

● Weaknesses and threats:

- The PI needs to secure funding for the coming years

- The international visibility of the team needs to be increased

● Recommendations:

- The proposal appears too broad for the current size of the group. A more focused approach is recommended.

- Further financial support is required to increase the size of the group and to develop specifc aspects of the proposal.

- Participation to international meeting needs to be increased

Team 10 : DNA repair and nuclear dynamics (LDNR)

Name of team leader: Ms Karine DUBRANA

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions		0	
N2: Permanent EPST or EPIC researchers and similar positions		1	1
N3: Other permanent staff (without research duties)		0	
N4: Other professors (PREM, ECC, etc.)		0	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		2	2
N6: Other contractual staff (without research duties)		1	
TOTAL N1 to N6		**4**	**3**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		1

• Detailed assessments

Assessment of scientific quality and outputs

During the last five years, the team leader first developed a cell biology study to assess in human cells the nuclear localization of chromosomes upon telomere loss. A collaborative paper in JCS (2010) was published (co-corresponding author). The team leader then joined Institut Curie, Paris) to study the processing of irreparable double strand breaks in budding yeast. This work was a follow-up of papers published as she was a postdoc (JCS and Science). Interesting results were obtained that are not published yet. She has now settled a novel team that has started novel projects that are still at early but very promising stages.

Assessment of the unit's academic reputation and appeal

Ms Karine DUBRANA obtained a young group leader position at CEA. Significantly, DUBRANA gained one of the highly prestigious ERC starting grants (2012-2017). This funding should allow her to establish herself as an independent group leader. The ERC grant should enhance the visibility and attractiveness of the Dubrana group for potential postdocs and PhD students. Moreover, Ms Karine DUBRANA has been collaborating with leaders in the field and she established good local collaborations which should facilitate the successful start of her research program.

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

As a newly-established group, the LDNR still need to establish interactions with the social, economic and cultural environment of the unit.

Assessment of the unit's organisation and life

With one technician, two PhD students and two postdocs, this new group has already reached the critical mass required to perform the planned project.

Assessment of the unit's involvement in training through research

Since the creation of the LDNR, two master students, two PhD students and two postdocs have been hired, which is quite significant, considering that the group was created less and a year ago.

Assessment of the five-year plan and strategy

The planned project is innovative and important. Good funding was obtained. The necessary infrastructure is available, collaborative teams have been identified and two PhD students, two postdocs and one technician were hired. Thus the group has a good size in order to excel in research. Overall, Dubrana seems well positioned to successfully pursue the planned research.

It is planned to (1) define how nuclear organization impacts on detection, processing and repair of double-stranded DNA breaks; (2) use proteomics and genetic screens to identify pathways that are responsible for relocalization of damaged DNA; and (3) study chromatin mobility in response to damage by light microscopy.

Conclusion

● Strengths and opportunities:

- Dubrana has all that is required to succeed with her research program. Funding (ERC grant), students, postdocs and a good research environment

● Weaknesses and threats:

- Although the research proposal is well conceived, its successful implementation will require very good collaborators

- Recommendations:

- No recommendations at this stage, the Dubrana's group should develop very well in the coming years

Team 11 : Telomeres and chromosome repair (LTR)

Name of team leader: Mr Stéphane MARCAND

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions		0	
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.)		0	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		1	1
N6: Other contractual staff (without research duties)		0	
TOTAL N1 to N6		**3**	**2**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		0

• Detailed assessments

Assessment of scientific quality and outputs

During recent years, the team of Mr Stéphane MARCAND has pioneered the characterization of chromosome end capping in *Saccharomyces cerevisiae*. The team's research is highly relevant to the understanding of genome stability and cancer development, as telomere fusions do occur during certain stages of tumorigenesis. The team published three highly elegant papers (Gene Dev 2008, Gene Dev 2010, EMBO J. in press). The lab demonstrated that telomere protection from end fusion events relies on Rif2 and Sir4, both of which are recruited to the telomeric DNA via Rap1. In addition, the DNA binding domain of Rap1 also contributes to protection from end fusion by the non-homologous end joining pathway. It was also discovered by Mr Stéphane MARCAND that dicentric chromosomes that contain telomere-telomere fusions, often break at these fused telomeres during mitosis. This therefore may represent a rescue pathway to separate fused chromosomes without causing genome rearrangements. Finally it was discovered that the SUMO-targeting ubiquitin ligase Uls1 is involved in telomere protection possibly by clearing telomeres from non-functional poly-SUMOylated Rap1 molecules.

Assessment of the unit's academic reputation and appeal

Over the past decade, the PI has published at least one article in a high-impact journal every second year, which is noticeable considering the very small size of his team. The PI is very well known in the telomere field and is frequently invited for seminars and oral presentations at international conferences. Stéphane Marcand is also part of the Epigensys european network. He acts as reviewer for prestigious journals (EMBO J, PLOS Genet, PNAS, Genetics, Genes Dev) and funding agencies (ANR, HFSP, CRUK). This group is well funded, with two successive ANR Blanc (2006-2011 and 2012-2015) and three ARC grants.

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

The research projects developed in the LTR group are very fundamental and have therefore limited immediate impact on the social, economic and cultural environment.

Assessment of the unit's organisation and life

A staff scientist has recently left and the size of the group is becoming critically small. However, during the past decade, Mr Stéphane MARCAND has demonstrated his ability to generate important articles with a very small group.

Assessment of the unit's involvement in training through research

The team leader is involved in a master course on DNA repair and telomeres at ENS Cachan. The lab has trained one PhD student since 2007.

Assessment of the five-year plan and strategy

It is planned for the coming years to further elucidate the mechanism of telomere protection from non-homologous end joining and to unravel how breakage of telomere fusions is mediated during mitosis. In the first part of the project, the LTR team will follow on earlier work to determine how telomeric factors such as Rif2, Sir4 and Rap1 cooperate to prevent NHEJ at telomeres. In particular, they will focus on newly-identified domains of Sir4, in collaboration with Ms Isabelle CALLEBAUT (CNRS, Paris VI) and Ms Karine DUBRANA (Team 10). The second research theme concerns the identification and characterization of specific regions of the genome that are prone to breakage when dicentric chromosomes are formed by telomere fusion. Unpublished evidence from this team indicates that chromosomes preferentially break at centromeres when fused telomeres are excised and that cells blocked in anaphase do not break dicentric chromosomes. These observations raise important questions regarding the enzymatic activity that cleaves DNA at specific sites. State-of-the-art techniques such as time-lapse microscopy (in collaboration with Julie Cooper, CRUK) and high-resolution mapping of chromosome breaks will be used in combination with powerful molecular genetics tools to address these questions.

Overall, the five-year research plan is very solid and the chances of success are very high. Both of these research themes are highly interesting and important. The laboratory is in an excellent position in continuing making highly original contributions.

Conclusion

- Strengths and opportunities:

- Excellent hypothesis-driven research

- The research topic is very good and the team highly capable

- This group has proven its ability to make original and highly relevant publications over the years

- Well-funded team

- Weaknesses and threats:

- Small size of the group (1 technician, 1 PhD student, 1 postdoc)

- Recommendations:

- An increase in laboratory size might further strengthen the team and enhance the output

Team 12 : Functional genome exploration (LEFG)

Name of team leader: Mr Claude GAZIN

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions		0	
N2: Permanent EPST or EPIC researchers and similar positions		2	2
N3: Other permanent staff (without research duties)		2	
N4: Other professors (PREM, ECC, etc.)		0	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		0	
N6: Other contractual staff (without research duties)		0	
TOTAL N1 to N6		**4**	**2**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		0

• Detailed assessments

Assessment of scientific quality and outputs

This is a recently-established independent group (since Jan. 01, 2009) consisting of three researchers (including the group leader) and two technicians.

During his work at UMass Med, the team leader made the discovery of a RAS-driven mechanism of epigenetic silencing. This was uncovered in an elegant screen for factors that mediate RAS-dependent pro-apoptotic Fas suppression and then extended to other factors epigenetically silenced in RAS-transformed cells. The concept of mutated oncogenes controlling epigenetic modifications was entirely novel and has had a significant impact in the field of oncogene-driven tumorigenesis since its publication in Nature in 2007.

Since establishment of his own independent research group, the team leader has initiated new projects and one is listed as completed. Recently published work (PLOS Genetics 2013) on synthetic lethality screens in cells carrying p53 alterations was carried out in collaboration with his previous lab. He is both joint first author and joint corresponding author to this publication.

In an attempt to identify druggable targets for cancer therapies, the lab has established cost-effective genome-wide shRNA screening conditions in human cells and next generation sequencing. These techniques will be instrumental in identify synthetic lethal interactions with tumor-promoting mutations in RAS and BRCA1.

Assessment of the unit's academic reputation and appeal

The group is proficient in state-of-the-art high-throughput technologies, including shRNA screens, ChIP-seq and tandem affinity purification. As such, it is highly appealing to scientific recruitment and external collaborations. Several such collaborations have already been established and some led to joint publications. The group leader is invited to speak at national and international conferences and participates to the MIT-France program.

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

Activation of the RAS pathway plays a central role in melanoma progression and metastasis. Equally, BRCA1 mutations are associated with a high percentage of inherited breast cancers and are often detected in sporadic cancers. Thus, the work in identifying cell growth suppressors in the context of both these genetic alterations is highly relevant to cancer. The lab has already established contacts with clinicians who will help translate the results of the basic research carried out in the lab into clinical output. In addition, the team leader is a co-author on a patent on use of effectors of RAS-mediated silencing and has contributed to the development of a software for the analysis of next generation sequencing data.

Assessment of the unit's organisation and life

This group is actively involved in collaborations locally and with international institutions. However, the group is totally dependent on these external collaborations to develop its projects. This may represent a serious threat for its viability as an independent research group.

Assessment of the unit's involvement in training through research

Mr Claude GAZIN has contributed to the training of MSc students from French academic institutions and MIT. However, the group does not currently host any PhD students or postdocs.

Assessment of the five-year plan and strategy

The five-year research plan examines basic and important questions in tumor progression and resistance to therapies, including ionizing radiation. The group leader has a strong background in high-throughput screens and is planning to apply these and related technologies to further decode the RAS-dependent epigenetic program driving tumorigenesis. In addition, in collaboration with colleagues, Mr Claude GAZIN is planning to identify synthetic lethal interactions in cells lacking DNA repair factors (e.g. BRCA1), known to underline susceptibility to breast and ovarian cancer.

In the first part of the proposal, the focus is on a shRNA screen performed in two isogenic melanoma cell lines, which differ in expression of oncogenic RAS. The screen will identify factors which specifically suppress growth of RAS-expressing cells, when depleted. These are factors that can potentially drive melanoma metastasis *in vivo*. The plan proposes a coherent set of analyses for hit validation and evaluation of the physiological relevance of the uncovered interactions, including contribution to the RAS-mediated epigenetic silencing program and tumor growth in xenograft models. This approach is original and the group leader is planning to perform both the screen and analysis with own resources.

The second part describes a set of shRNA screens for synthetic lethal interactions cells lacking DNA repair factors BRCA1, BLM and FANC family proteins. This is a rather broad approach and will be performed in collaboration with three other groups. It is unclear whether Mr Claude GAZIN'S laboratory will contribute mainly technologies and data analysis to the screen itself, as it is stated in the proposal that the physiological relevance of the hits will be determined by the collaborating laboratories. Nevertheless this joint effort has a good potential to generate a list of novel targets and to develop novel therapeutically modalities for cancer.

A separate section is focused on screens for factors that mediate resistance of BRCA1-deficient cells (and possibly tumors) to cisplatin, PARP inhibitor and radiation therapies. It is unclear how informative the outcome of these screens will be, as there is already extensive evidence that resistance is largely acquired through revertant mutations in BRCA1 gene that potentially restore DNA repair. This part of the proposal requires strong preliminary data in order to be convincing.

Overall, this five-year plan builds on the unique expertise of Mr Claude GAZIN to exploit state-of-the-art genomic assays in a cost-effective and insightful way. However, most of the proposed projects rely on external collaborations, which raises the question of the sustainability of the team as an independent group.

Conclusion

● Strengths and opportunities:

- The strengths of this group are the proven exceptional research ability of the group leader and the recently acquired expertise in cutting-edge technologies. As such the group is well posed for excellent collaborative work to advance the understanding of tumor initiation, progression and response to radiation therapy.

● Weaknesses and threats:

- Mr Claude GAZIN maintains a strong collaboration with the lab of Mr Michael GREEN at UMass, where he achieved his postdoctoral training. This poses the potential danger that the US group may be primarily recognized for the outcomes of this collaboration. Also, a large part of the future proposal relies on collaborations with other teams, although Mr Claude GAZIN will contribute invaluable technological support to these collaborative projects.

● Recommendations:

- Mr Claude GAZIN should gradually become integrated into the group of Mr Paul-Henri ROMEO. The team of Mr Claude GAZIN will benefit from such merger, as it will acquire a structure and funding to develop state-of-the-art technologies, which will facilitate future collaborations with several of the groups within the unit. It should be noted that Mr Claude GAZIN has an excellent scientific potential and is able to develop his ideas independently. In the future it is anticipated that the group leader will seek funding from external sources to establish his own independent research program.

5 • Conduct of the visit

Visit dates:

Start: Tuesday 29 January 2013 at 2:00 pm

End: Thursday 31 January 2013 at 2:30 pm

Visit site:

Institution: CEA / Fontenay-aux-Roses

Address: Route du Panorama, F-92265 Fontenay-aux-Roses

Conduct or programme of visit:

The visit was well prepared and the evaluation took place in excellent conditions. A detailed document was provided in advance, containing executive summaries, results and scientific projects for the unit and individual teams. The evaluation of this document was complicated by the fact that some of the documents and tables were only provided for the five UMR 967 teams. Additional information concerning the past activity of the seven other teams was requested by the committee and was provided before the visit. On site, the visit was executed smoothly and without any problems, with sufficient time to organize separate discussions with directors, group leaders, staff scientists, technicians and non-permanent scientists (students and postdocs). No visit of the labs was planned and the visit of platforms (irradiation, cell sorting, imaging) was cancelled due to lack of time.

6 • Statistics by field: SVE on 10/06/2013

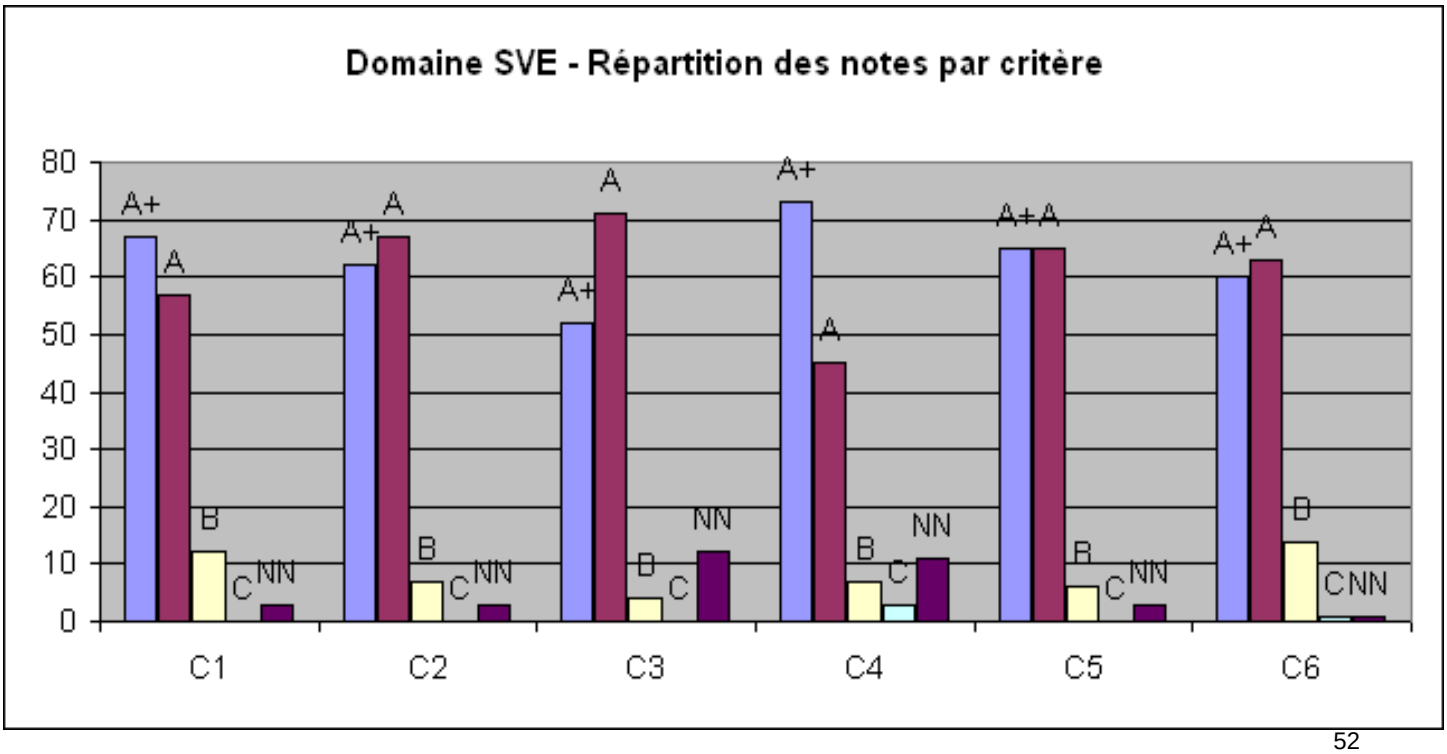
Grades

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	67	62	52	73	65	60
A	57	67	71	45	65	63
B	12	7	4	7	6	14
C	0	0	0	3	0	1
Non Noté	3	3	12	11	3	1

Percentages

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	48%	45%	37%	53%	47%	43%
A	41%	48%	51%	32%	47%	45%
B	9%	5%	3%	5%	4%	10%
C	0%	0%	0%	2%	0%	1%
Non Noté	2%	2%	9%	8%	2%	1%

Histogram



7 • Supervising bodies' general comments

université PARIS DIDEROT PARIS 7

Le Président

P/VB/RL/NC/YM – 2013 - 080
Paris, le 15 avril 2013

M. Pierre Glaudes
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

S2PUR140006437 - Stabilité génétique, cellules souches et radiations - 0751723R

Monsieur le Directeur,

Je vous remercie, ainsi que les membres du comité de visite, pour l'envoi du rapport d'évaluation concernant le «iRCM», rapport qui souligne le très bon niveau scientifique de l'unité dans l'ensemble, comportant une grande proportion de groupes excellents dotés d'une visibilité internationale. Mais aussi la réorganisation réussie de l'UMR 967, avec une amélioration significative de l'impact de ses activités de recherche.

Je me réjouis également des commentaires très élogieux qui sont portés sur le fort attrait pour les étudiants et post-doctorants, en dépit du relatif isolement géographique de l'unité, sur la large place faite aux femmes parmi les chercheurs et sur la politique active mise en place pour les jeunes chercheurs.

Enfin, l'établissement et ses partenaires tiendront compte, à la hauteur de leurs moyens, du point mentionné par le comité concernant la faiblesse de la structure administrative actuelle pour soutenir les 12 équipes de recherche.

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

Vincent Berger

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SORBONNE PARIS CITÉ
RECHERCHE ENSEIGNEMENT SUPÉRIEUR

April, 12th 2013

We would first like to thank the members of the AERES committee for their work, their overall faithful evaluation of the scientific production, activity and organization of our research unit and their positive comments concerning the project they have evaluated.

Concerning the Unit proposal

We would like to clarify the relationship between the Institute of Cellular and Molecular Radiobiology (iRCM) and our UMR proposal. Our project is not to create, as stated in the report, "a novel Institute of Cellular and Molecular Radiobiology that will result from the fusion between UMR967 and the former UMR217". Our project is rather to create within the iRCM a new UMR entitled **"Genetic stability, Stem cells and Radiation"** that will be under the supervision of **Inserm**, **CEA**, **Université Paris-Diderot** (**Paris 7**) and **Université Paris-Sud** (**Paris 11**). iRCM, under the sole supervision of CEA, comprises several other important teams that are not part of the present proposal. Therefore, "**iRCM**" as to be changed for "**UMR: Genetic stability, Stem cells and Radiation"** in all the relevant instances from page 1 to 8.

As for the expert committee members, the representatives of the unit's institutions and bodies were Ms Nicole Haeffner-Cavaillon and Ms Laurence Parmentier for Inserm, Mr Gilles Bloch for CEA, Mr Marc F. Benedetti for Paris-Diderot and Ms Annelise Bennaceur-Griscelli for Paris-Sud.

Concerning the teams of the unit

Team 1: Development of the Gonads

Recruiting full time researchers is critical for this team and this point is taken into account as Dr. Emmanuelle Martini, who is a full time CEA researcher, has now joined this team. Thus, for the 2014-2018 period, there will be at least one permanent researcher and this was not included in our written proposal.

Team 2 : Gametogenesis, Apoptosis, and Genotoxicity

Most of the comments of the AERES committee are relevant, but some points need to be clarified.

"Past and current academic grants were mostly obtained by the previous group leader"

This comment is inaccurate as the two PIs of LGAG have their own grants for more than 10 years (EDF and ARC in the past).

"The team was restructured to anticipate this evaluation and Isabelle Allemand

took the lead in 2009"

Our team is structured around the two PIs for more than 10 years and I. Allemand was already at the head of the team in the past UMR566 i.e. before UMR967 was created in 2009. Even if the team did not appear as an administrative entity for a time, the team was in fact financially and scientifically autonomous.

Team 4 : Neural stem cells and radiation

"This group has made significant contributions to the field of neuronal stem cell activation, growth and responses to ionizing radiation,…", including 12 publications in good journals (EMBO J, Nucleic Acids Res, Stem Cells, Cell Mol Life Sci), a patent and 11 other publications as collaborations.

The group has also recently published 1 EMBO Mol Med that was in press at the time of the oral presentation.

"In addition, work in the lab is focused on telomere maintenance and has shown that about 30% of human gliomas rely on pathways of telomere elongation alternative to telomerase (alternative lengthening of telomeres, ALT)"

Although it is true that this phenomenon has been reported previously, this team has characterized the first human glioma stem-like cell line with an ALT phenotype that represents the first ALT glioma cell line described to date.

"Assessment of the unit's organization and life: No information provided on this aspect" and "Moreover, it is not clear who and how many people are involved in each research"

This information may be found in the "Fiches individuelles" and was given during the oral presentation.

Team 6 : Keratinocyte stem cells, regenerative potential and genome stability

Workforce Table1

N2 permanent researchers: 3

N3 other permanent staff: 3

Total: 6

Workforce Table 2 (30/06/2012)

Doctoral students: 2

Theses defended: 6

Postdoctoral: 1

HDR: 2

Qualified supervisors: 3

Team 11 : Telomeres and chromosome repair

Workforce Table 2 (30/06/2012)

Doctoral student: 1

Paul-Henri Romeo

Monsieur Pierre GLAUDES
Directeur de la section des unités de l'AERES
20, rue Vivienne
75002 PARIS France

Fontenay-aux-Roses, le 25 avril 2013
Objet : S2PUR140006437 - Stabilité génétique, cellules souches et radiations - 0751723R
N/Réf. : DSV/DIR/2013-157/ADLC/guc

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport d'évaluation de l'unité mixte de recherche « Stabilité génétique, cellules souches et radiations » dirigée par Paul-Henri ROMÉO dont l'université Paris-Diderot, l'Inserm, le CEA et l'université Paris-Sud exercent la tutelle. Le comité de visite a réalisé un remarquable travail d'évaluation et souligne la grande qualité scientifique de cette unité et le potentiel de visibilité que la réorganisation proposée doit lui apporter.

Le CEA est à la fois tutelle scientifique et hébergeur de cette unité de recherche localisée sur le site de Fontenay-aux-Roses. C'est à ce titre que je souhaite apporter quelques éléments d'éclairage à la remarque globale du comité de visite concernant la « complexité des procédures du CEA ». La localisation de cette unité sur un site CEA induit en effet des contraintes d'accès au site, propres à tous les sites du CEA, qui engendrent parfois des désagréments aux chercheurs. Le statut d'EPIC du CEA lui confère des avantages complémentaires à ceux des autres tutelles de l'unité. Les facilités des règles financières en termes d'avance de trésorerie, de négociations des achats ou encore de réactivité à la mise en place de contrats de recherche et d'accueil de personnel contractuel sont des atouts indéniables pour les unités de recherche du site.

.../...

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Direction des sciences du vivant
Le Directeur

Par ailleurs, l'unité de recherche et les 12 équipes qui la constituent bénéficient du support administratif mis à disposition par le CEA à l'Institut de radiobiologie cellulaire et moléculaire (IRCM) auquel est rattachée cette unité.

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

Gilles BLOCH
Directeur des sciences du vivant

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Le Président de l'Université Paris-Sud

A

Monsieur Pierre Glaudes
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Orsay, le 26 Avril 2013

Réf : 67/13/JB/EA/NH

Objet : Evaluation de l'UMR 967 « Stabilité génétique, cellules souches et radiations »

Monsieur le directeur,

Je tiens à remercier le comité AERES pour la qualité et la précision de son travail d'évaluation de l'UMR 967, dont l'Université Paris-Sud est tutelle secondaire. Nous avons étudié votre rapport avec attention dans la mesure où l'unité demande à notre université de continuer à exercer cette tutelle pour les cinq prochaines années.

Nous nous associons aux remarques transmises par Monsieur Paul Henri Roméo, directeur de l'unité et souhaitons notamment que soit mentionnée la présence lors de la visite du comité, du Professeur Anne-Lise Bennaceur-Griscelli, représentant l'Université Paris-Sud.

Recevez, Monsieur le Directeur, l'assurance de ma considération.

Le Président de l'Université Paris-Sud

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Pr Jacques BITTOUN

Copie : Mr. Gille Bloch, Directeur des Sciences du Vivant, CEA
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Prof. Vincent Berger, Président de l'Université Paris Diderot
Dr Paul-Henri Roméo, Directeur de l'UMR 967
Prof. Serge Bobin, Doyen de la faculté de Médecine