DIG-CANCER - Dynamique de l'information génétique : bases fondamentales et cancer

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Dynamique de L'Information Génétique: Bases Fondamentales et Cancer
DIG-CANCER

Under the supervision of the following institutions and research bodies:

Institut Curie

Centre National de la Recherche Scientifique

Université Paris6 - Pierre et Marie Curie

January 2013

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

Research Units Department

President of AERES

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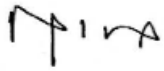


Pierre Glaudes

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 overall assessment and the following grades:

● Grading table of the unit: Dynamique de L'Information Génétique: Bases Fondamentales et Cancer DIG-CANCER

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

● Grading table of the team: Functional organization and plasticity of mammalian genomes

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

● Grading table of the team: Telomeres and Cancer

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

● Grading table of the team: Genome Instability and cancer

C1	C2	C3	C4	C5	C6
NN	NN	NN	NN	NN	nn

● Grading table of the team: Recombination and genome instability

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

- Grading table of the team: Genetics of Tumor Suppression

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

- Grading table of the team: Non Coding RNA, epigenetics and genome fluidity

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

Evaluation report

Unit name:	DYNAMIQUE DE L'INFORMATION GENETIQUE : BASES FONDAMENTALES ET CANCER
Unit acronym:	DIG-CANCER
Label requested:	UMR
Present no.:	UMR3244
Name of Director (2012-2013):	Ms Michelle DEBATISSE
Name of Project Leader (2014-2018):	Mr Arturo LONDOÑO-VALLEJO

Expert committee members

Chair:	Ms Annick HAREL-BELLAN (DSV-CEA, Gif/Yvette)
Experts:	Mr Andres AGUILERA (Sistema de Información sobre Investigación - *Universidad de Sevilla*,Spain)
	Ms Agnès BERNET (Centre de recherche en cancérologie, Lyon, representative of CNU)
	Mr Paul EDWARDS (Cambridge University, UK)
	Mr Marcel MECHALI (IGH-CNRS, Montpellier)
	Ms Anne PEYROCHE (DSV-CEA, representative of CoCNRS)
	Mr David SHORE (University of Geneva,Switzerland)
	Mr Michel WERNER (DSV-CEA, Gif/Yvette)

Scientific delegate representing the AERES:

Mr Jacques HAIECH

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

Ms Delphine DUPREZ (UPMC, Paris 6)

Mr Domenico LIBRI (CNRS)

Mr Daniel LOUVARD (Institute Curie)

1 • Introduction

History and geographical location of the unit:

The Unit is the continuation of the laboratory headed by Mr Bernard Dutrillaux, who retired in 2002. It has been headed by the current director since then. The unit has been renewed in 2004 and 2008, as a CNRS/University Pierre et Marie Curie supported laboratory. Between 2004 and 20012, 3 young groups were recruited. The committee would like to emphasize the remarkable evolution of the unit the current director took the responsibility: She was instrumental in giving to the unit its outstanding scientific successes, its remarkable international reputation and its very high attractivity.

The unit is located within the Paris campus of the Curie Institute. The labs have been renovated and are well designed. However, the unit is located on two different floors in the same building on the Curie Institute's campus.

Management team:

The current unit head is going to retire in three years. As a consequence, a new leader has been chosen as project leader for the next five-year period. This new unit head seems to have the scientific maturity and the generosity required for managing this unit. He will be helped by the lab council, which includes the team leaders and elected members representative of the different categories of personnel. The lab council has approved the choice of this new director of the unit. The council, however, meets only twice a year, which might not be sufficient to really impact on the management of the laboratory.

AERES nomenclature:

SVE1_LS2

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	7	7	7
N2: Permanent researchers from Institutions and similar positions	5	5	5
N3: Other permanent staff (without research duties)	14	14	
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)			
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	6	6	6
N6: Other contractual staff (without research duties)	1	1	
TOTAL N1 to N6	33	33	18

Percentage of producers	***100 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	9	
Theses defended	12	
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	6	6

2 • Assessment of the unit

Strengths and opportunities:

The unit is generally very successful and has an excellent international reputation in the field of DNA replication and recombination. The laboratory has made several seminal discoveries. The director has created a dynamic and challenging scientific environment and was successful in attracting young PIs, some being outstanding. The laboratory is moving forward and is hosting very promising young groups. The incoming director should be able to take over.

Weaknesses and threats:

The departure of the current director and and a senior PI, who are leading the laboratory toward excellence, will create a serious threat for the future of the unit.

Recommendations:

A new team should be hired soon. The future director should decide on a scientific strategy within the frame of the Curie Institute and start searching as soon as possible.

3 • Detailed assessments

Assessment of scientific quality and outputs

The unit has made several seminal discoveries and has an outstanding scientific production, with 71 papers since 2007, among which many are in the best journals such as *Cell, Nature, Nat. Struct. Mol. Biol., Genes & Dev., EMBO J, PNAS* etc..

Assessment of the team's academic reputation and appeal

The unit has an excellent international reputation. The unit has numerous excellent collaborations worldwide. It is well renowned, members being invited regularly to international meetings, and being awarded various prizes and honors. The unit is remarkably attractive for students and post-docs from abroad. It is also attractive for senior people, and it is important to note that three sabbatical visitors have been hosted by the laboratory in the past 5 years, including a Nobel Prize winner.

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

Even though the Unit is working on very basic aspects and doing very fundamental research, the unit has created and shelters a start up company, which exploits an in house patent. In addition, the unit has very active interactions with the clinics and develops translational projects.

The unit as a whole is also deeply involved in teaching at the university. In addition, several groups participate in the organisation of international courses of very high quality.

The unit is also involved in conveying scientific messages to lay public, in particular in the frame of the Curie Institute .

Assessment of the unit's organisation and life

The unit has a general scientific meeting every month, and each group also holds internal meetings every week. The technicians are welcome to participate. In addition, the unit also organized a highly appreciated laboratory retreat, which will be reproduced by the end of the year 2013.

However, the committee noted the lack of a journal club or other form of discussion forum for the students and post-doctoral fellows, which should be easy to organize given the homogeneity of the groups' research interests.

A laboratory council has been constituted, but apparently it does not meet very often, which seems to result in poor communicaton of important decisions to the laboratory personnel.

The committee noted that the Sauvadet law has put tremendous pressure on the non-permanent personnels. Under these difficult conditions, the unit management team must be proactive in planning the future of these personnels and in warning them well in advance about the difficulties lying ahead. An improvement in that respect might come from good communication with the human relationship department of the Institute.

Concerning the permanent technical personnel, the promotion is slow, even though the managenemt is doing its best to improve that. Concerning the young assistant professors, the committe noted that the Unit has been extremely successful in obtaining positions (4 new assistant professors) in the past years. However, the commmittee is under the impression that an insufficient proportion of them was awarded with an HDR, which may be due in part to the stringent conditions for HDR at the UPMC but that blunts the capacity of the unit in hiring PhD students. Thus, the Committee advises to help the promotion of assistant professsors (MCU) in the unit.

The personnel received the necessary training and has all opportunities to get trained in various domains, from learning English to acquiring sophisticated technologies.

The unit is well funded, by the Curie Institute and to a lesser extent by the CNRS. The unit does not receive money from the University, because it is located off campus, but the committee noted that UPMC provided a strong support in the form of assistant professor positions (4 in the last 5 years). The bulk of the money comes from external sources, and the unit is extremely successful in raising grants (close to 6.5 Millions euros from various international and national institutions in the past 5 years, including an ERC starting grant). There is a good financial solidarity within the Unit.

The members of the Unit profit from a very rich technological environnent, with excellent platforms, some of which being directly managed by a member of the unit (such as the New generation Sequencing (NGS) platform).

Assessment of the unit's involvement in training through research

The unit is deeply involved in teaching, at the University and within the Curie Institute. Members of the Unit created - are managing and are teaching in - 4 different courses (Genetics of eukaryotic cells - 60h, 40 students; Genetics of cancer- 60h, 50 students; Initiation to Biostatistics - 30h, 40 students; Bench course Molecular and genetics techniques, 60h, 120 students). The unit has an original setting in that its members form a true pedagogical team, also providing teaching in various external institutions, including the Pasteur Institute.

The unit trained many students at various levels during the past 5 years (9 M1, 24 M2, et 14 various internships). Moreover, 12 PhDs were defended. All students benefit from an external thesis committee that helps them in their strategic decisions. The students are enrolled in the ED515 (Doctoral school Life complexity located at Paris 6). The quality of the science really contributes to the excellent training of these students, and the unit is highly rated in that respect, both in quantity and in quality.

Assessment of the five-year plan and strategy

The scientific strategy is extremely well thought, in the follow up of the excellent research done previously. Even the retiring people are proposing scientific plans in line with the timing of their retirement. The committee noted the general coherence of the scientific projects. The committee is confident in the general success of the proposed projects.

The departure of two senior scientists, who are leading the unit towards excellence, will create a serious threat for the future of the unit. It will be a challenge for the unit to find people as good as they are. A new team should be hired soon. Whether it should be a bioinformatics group or a biology group working on the main topic of the laboratory was a very debated issue, both among the group leaders of the unit and among the committee menbers. Given the future departure of these two senior scientists, the committee believes that it would be a good choice to reinforce the biology forces of the lab.

The committee, however, also agrees that getting more bioinformatics forces is essential, but it might be more beneficial to hire bioinformaticians in the different groups. All these issues need to be addressed in the context of the whole Curie campus.

The departure of the unit director, who is a University professor, also raises the question of the future relationship of the unit with the UPMC. She will support the promotion of one of the assistant professors as full professor.

4 • Team-by-team analysis

Team 1 : Functional organization and plasticity of mammalian genomes

Name of team leader: Ms Michelle DEBATISSE

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	2	2	2
N2: Permanent EPST or EPIC researchers and similar positions	1	1	1
N3: Other permanent staff (without research duties)	2	2	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2	2
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	7	7	5

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

• Detailed assessments

Assessment of scientific quality and outputs

The team has an international reputation in the field of genome stability and DNA replication. Over the last years, the group focused on the dynamics of DNA replication and its relationship with the instability of DNA fragile sites. This laboratory was among the first to show how cells can adapt to poor growing conditions, particularly under conditions of nucleotide depletion, by activating latent replication origins. They also confirmed a relationship between chromatin loops and the organization of replication units.

In particular, the team 1 has made strong contributions in the last years that have provided important concepts in the fields of DNA replication from a genomic perspective and common fragile sites (CFSs). They have introduced new ideas on the way replication fork speeds, influences the activation of latent pre-replication origins distributed around a main origin that is initially fired. They have shown that latent origins in the AMPD2 locus are recruited within minutes when forks slow down, suggesting that these forks serve to compensate replication difficulties generated by replicative stress to allow completion of replication. Switching from slow to fast moving forks decreases the density of initiation events. They also showed that hyper-acetylation affects the usage of replication origins, by decreasing the deoxynucleotide pools, leading to the recruitment of latent origins. This does not seem to depend on histone acetylation levels from their analyses, even though other work suggested in the past that it could be the case. Such conclusions derive from studies using trichostatin A, an inhibitor of deacetylases, but which is known to produce, likely as a consequence of this, an alteration in the expression of 2-5% of human genes. Concerning the way fork movement is regulated by the replication checkpoint, they have shown that deficiency of Chk1 limits dNTP availability slowing down replication fork movement. As a consequence, initiation density increases by the "compensation" mechanism. This is an interesting and novel view that fits with the idea that Chk1 inactivation de-represses latent origins. It seems that this feature may be common to other proteins of the DNA damage response such as Rad51. More work is still needed to know how this whole mechanism works to sense and control latent origin activation, in any case.

A second major achievement of this group in the last years concerns Common Fragile Sites (CFS) instability. They show that fragile sites correlate with long DNA regions that are replication origin-poor, and therefore more vulnerable to replication failures. Therefore, their studies on CFSs have revealed that these are regions difficult to replicate. However, it seems clear that this is dependent on cell type, as FRA3B behaves as CFSs in lymphocytes but not in fibroblasts, and using the polymerase inhibitor aphidicolin, the delay in fork progression is the same in the bulk genome as in the CFS regions. They have shown that, in fibroblasts, the density of initiation is the same in the core FRA3B as in the bulk genome, whereas this is not the case in lymphocytes, confirming that replication initiation-poor regions are the basis for fragility. Interestingly, similar features are observed in other fragile sites. The group has new data showing that mitotic entry with under-replicated CFSs causes chromosome breakage for which protection is crucial for CFS integrity. More recently, the group also showed that the checkpoint response could vary according to the degree of replication fork slowing. The discovery of this new role of replication origin-poor regions in promoting fragile sites is a recent major finding of this group.

Assessment of the team's academic reputation and appeal

The research achieved by this group in the last years is impressive in terms of quality, originality and impact. It was always inspired by really new concepts. The team leader is regularly invited to the most important meetings in the field of DNA replication and repair. This work has been published in excellent journals, such as Nature 2008 & 2011, Nat Str. Mol. Biol. 2011, EMBO R 2010 and has given rise to a provoking review in Trends Genetics 2011. This together with the invitations to international meetings such as ISCN-GRI in Japan, ISCO 2012 in Spain, Cold Spring Harbor 2011 in USA, Jacques Monod in France, the Brazilian Biochemistry Society in Brazil 2007 and others more specialized in Japan 2010 plus conferences at international centers in New York, Erlangen (DE), etc. gives an idea of the impact of the excellent research activity of this group.

The group consists of 9 people, including a DR2 with a good CV who participates in many of the contributions of the group. The group has in addition two technicians, 2 postdocs and 2 PhD students. It is a well-equilibrated group, with an excellent productivity with, in the last years, very strong publications in the field. The team leader was elected EMBO member in 2011.

The research of team 1 is novel, very well thought out, with clearly defined objectives, and very sharp experimental approaches. The results are very well cited and accepted in the field.

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

Not applicable

Assessment of the team's organisation and life

Not applicable

Assessment of the team's involvement in training through research

Not applicable as the involvement of the training is done at the level of the overall unit.

Assessment of the five-year plan and strategy

They plan to evaluate the role that transcribed chromatin has on CFSs. This comes from the observation that 43 out of 49 CFS are in extremely long genes (<300 kb); however apparently there is no correlation between fragility and expression of genes in their results. It is not indicated how this conclusion was reached. Their hypothesis is that chromatin structure and nuclear positioning is a major determinant of fragility. For this, they plan to use three different approaches. In the first one, they will determine the boundaries of replication timing domains hosting CFSs and compare them with the limits of the corresponding CFSs, for which they will include data about chromatin status. Special interest will be put into the analysis of the insulator protein CTCF and cohesins, as putative determinants in the definition of chromatin domains of replication. They expect to define the spatial organization of the domains by using long-range interaction maps generated by chromatin conformation capture. They consider the possibility that there are loop boundaries along domains hosting large genes. Experiments of FISH and 3D microscopy will be used.

In a second approach, they plan to determine the role of transcriptional regulators on fragility. For this, they will engineer in collaboration with a biotechnology company transcription regulators using a fusion with the DNA binding domain of TALE proteins that can be fused to other domains such as DSB endonucleases, as it has been done successfully in the past. Team 1 will make first a fusion with the VP16 transcription activator to establish the proof of concept. Then they will target acetylases or methyl-transferases that allow them to modify chromatin structure and determine the impact on fragility. To understand how transcription may modulate fragility in a chromatin-related manner, they will use the DT40 chicken system. They expect to manipulate the replication timing of specific regions by targeting cis-elements to determine the structural basis for replication origin firing. Finally to determine the impact that chromosome localization in the nucleus may have on the efficiency of replication origin, they will determine whether domains hosting large genes display particular nuclear localization. For this they will use genome-wide scale to determine the interactions between chromatin and the inner-nuclear membrane lamins using the DamID technique based on a Lamin B fused to the adenine methyltransferase Dam of E. coli.

This is an excellent project with new approaches using DT40 cells, which will complement strongly the work they do in mammals, and which we are sure will continue providing new clues about genome replication, regulation of initiation and chromosome fragile sites.

Conclusion

- Strengths and opportunities:

The team is doing an outstanding work, excellently focused. They made seminal discoveries of high impact, and have a strong international reputation.

- Weaknesses and threats:

No specific weaknesses have been noted

- Recommendations:

No specific recommendations have been forwarded by the committee.

Team 2 : Telomeres and Cancer

Mr Arturo LONDOÑO-VALLEJO

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	1	1	1
N3: Other permanent staff (without research duties)	2	2	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1	1
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	5	5	3

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

• Detailed assessments

Assessment of scientific quality and outputs

The group presently comprises the PI and seven additional researchers. This team has published well, and in several diverse areas, in the past 5 years and has now established itself as an up-and-coming force in the telomere biology field. Of particular note is a paper published in *Genes & Dev* in which team 2 describes novel strand-specific roles for the WRN helicase and the ssDNA-binding telomeric protein POT1 in telomeric DNA replication. These studies, which employed a very technically challenging Q-CO-FISH technique in telomerase positive cells allowed the first direct assessment of the role of the WRN helicase in these cells and provided surprising new insights into the strand-specific dynamics of telomere replication. This work also raised interesting questions regarding the cell's ability to tolerate DNA repliation stress at telomeres. A second notable publication reported on the replication timing of telomeres in normal human cells and its relationship with the sub-nuclear localization of chromosome ends (Arnoult et al. *PLoS Genetics*). Although these issues had been addressed previously, Team 2 has gone into much more detail, in particular showing for the first time that there is a much larger than previously thought sub-set of telomeres with peripheral nuclear localization and late replication. In addition, their studies provide the first direct insight into the sub-telomeric DNA sequence elements that confer these properties. In a third notable study (Draskovic et al, *PNAS*) team 2 provides the first direct evidence that PML bodies are in fact sites of telomere-specific clustering and recombination in telomerase-negative ALT cells. In addition to these publications where the PI is senior author, team 2 has also been involved in several collaborations, some of which have been published in very high impact journals (e.g. Ye et al. *Cell* (2010)).

Assessment of the team's academic reputation and appeal

Team 2 has clearly established himself, particularly during the past 5 years, as a significant new member of the telomere biology field. This is evidenced by invitations of the team leader and members of the team to several national and international meetings as well as now regular invitations to make oral presentations at the major biannual international telomere meetings (one at Cold Spring Harbor, the other an EMBO Conference, most recently held in France). Apart from this and the original articles cited above, team 2's members have also been actively involved in the writing of invited reviews in the field, again covering a wide area of telomere biology. As a result of all of this, team 2 now has wide visibility in this field, which is a significant accomplishment considering that this has been a highly active and competitive field for about 20 years now.

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

Not applicable

Assessment of the team's organisation and life

Not applicable

Assessment of the team's involvement in training through research

Not applicable

Assessment of the five-year plan and strategy

Team 2 has laid out an ambitious plan for the next 5 years, but one where the goals for the most part seem to be feasible and clear priorities have been set. As was the case during the previous review period, Team 2's research aims cover a remarkably wide range of topics in the telomere biology / cancer field. Nonetheless, his success during the past review period and the manner in which his proposed research was defended, particularly during the oral presentation and questioning that followed, are all encouraging.

Team 2 proposes to focus primarily on three areas: (1) RTEL function and mechanism in non-telomeric roles, (2) Continued study of mechanisms of telomere recombination in ALT cells, and (3) Contribution of telomere instability to cancer-related phenotypes. The first aim is based upon a series of quite interesting and unexpected observations some of which were presented in the written document, but others only in the presentation (and all apparently unpublished) clearly indicating that RTEL has roles outside of DNA metabolism. In particularly Londono showed compelling evidence that the protein is involved in aspects of RNA metabolism such as non coding RNA trafficking and RNP biogenesis, roles that were previously unsuspected. The proposed studies are carefully designed and thought out and are likely to break new ground, but may also clarify the role of RTEL in telomere biology. Some recent reports on this protein, though published in very prestigious journals, are less than convincing on some points and leave several open questions. However, since team 2 has apparently discovered a new aspect of RTEL function, the proposed studies may make a significant impact on the field without the need to directly counter the present published work. The second major aim also involves RTEL, as team 2 proposes to investigate the role of the protein in ABPs, and in particular in telomere recombination in ALT cells. In this proposal, team 2 points out that RTEL has only be directly associated with telomeres in ALT cells. Their ability to knock down RTEL expression by shRNAs in a number of different cell lines bodes well for the successful completion of the proposed studies. The final major aim deals largely with a characterization of a striking effect on miRNA expression induced by telomere-driven chromosome instability (a phenomenon well documented in the report but still apparently unpublished). Team 2 proposes that this regulatory effect is due to global changes in the "epigenetic landscape" of cells undergoing critical telomere shortening, and proposes to use ChIPseq methods to address this hypothesis. No specific details are given here, though the system they describe is certainly novel and would appear to be well worth further general characterization.

Overall, this is a solid plan that builds in a logical way on recent lines of research that team 2 has developed. In each of the different areas to be developed in the proposed projects there is strong reason to believe that novel insights will result. An important strength of the proposal is its originality.

Conclusion

- Strengths and opportunities:

Team 2 has published reasonably well during the past 5 years with three senior author papers appearing in relatively high profile journals (*Genes & Dev*, *PLoS Genetics* and *PNAS*), each covering distinct areas of telomere biology: novel strand-specific roles for the WRN helicase and the ssDNA-binding telomeric protein POT1 in telomeric DNA replication, telomere replication timing and its relationship to nuclear membrane proximity, and the role of ALT-associated PML bodies (APBs) in telomere recombination, respectively. Team 2 has also been involved in publications from numerous collaborations and written at least 6 reviews during this period. Team 2 also reported and presented a considerable amount of interesting, unpublished data, again on several different and quite diverse areas. Overall the published output is very good to excellent, but not outstanding.

One of the striking characteristics of Team 2's research program during this period is its diversity. There appear to be at least as many research areas as there are group members. Oddly, it is difficult to know whether this is a strength or a weakness (or both). On the positive side, Team 2's leader is clearly an imaginative scientist who seems to be able to find interesting avenues of research that are typically somewhat off the beaten path. This is particularly true of his more recent work on RTEL, but also the case for some of the disease related work (e.g. idiopathic pulmonary hypertension) and the discovery of altered miRNA expression in pre-crisis telomerase-minus cells. He thus has several opportunities to make unique contributions to the field, something that he has already achieved in the past review period. Another strength of the unit is the ability to interact positively with clinicians and clinical researchers on what could be loosely termed "translational" projects.

With regard to the team 2's international standing and the integration of team 2 within the unit, the signs are all very positive. Team 2 has now made a name in the telomere field in a relatively short period of time. Recent progress within team 2 seems to have a very positive slope, and this suggests that the team 2' stature in the field will only increase in the coming years. Team 2's leader has put together a very dynamic and high spirited group. Team 2 has also been very successful in collaborating with other groups, both within the unit and outside.

- Weaknesses and threats:

As mentioned above, one of team 2's strengths (diversity of research projects), carries with it significant risks. The most obvious danger is that by spreading the team's efforts over so many different projects, the team will fail to maintain a sufficient rate of progress in any one of these areas to remain competitive. However, the publication record so far indicates that this will probably not be the case. Nevertheless, the mammalian telomere biology field is highly competitive, with a large number of very strong labs often pursuing similar goals. Thus, as new opportunities arise (the identification and cloning of the RTEL helicase being a good example), groups will often concentrate their efforts on obtaining the first functional insights, with very high impact papers quickly following. In the case of RTEL, there has been a recent spate of papers from two other labs (published in *Cell, Science and Molecular Cell*). Much to his credit, team 2 's leader has taken a more open approach to the problem and has made several interesting observations regarding non-telomeric (or perhaps non telomere-specific) functions of RTEL related to ncRNA transport. Nevertheless, team 2 would be best advised to bring some of this work to publication as soon as possible. It is encouraging that team 2 proposes in the upcoming 5 years to focus his efforts somewhat more, with a particular emphasis on RTEL and on a very interesting miRNA regulatory phenomenon that team 2 has recently discovered in cells undergoing telomere-shortening induced chromosomal instability.

- Recommendations:

The committee would hesitate to advise Team 2 to become more focused on a small number of topics. Team 2 might actually be more effective working in the relatively dispersed way that it does now. Although it was not clear from the team 2's written report, during the presentation and the discussions that followed it became apparent that team 2's leader has a very strong grasp of many different areas in biology, and a level of enthusiasm and imagination that should allow team 2 to successfully pursue multiple projects. At the same time, team 2 must maintain a sufficient focus so that publications continue to appear at a good rate. From the written document and discussions it seems that team 2's leader is well aware of this, even though it also seems unlikely that any projects are going to be cut from his program.

Team 3 : Genome Instability and cancer

Name of team leader: Mr Bernard MALFOY

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		0	
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.)		0	
N6: Other contractual staff (without research duties)		0	
TOTAL N1 to N6		0	

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		

• Detailed assessments

Assessment of scientific quality and outputs

The team 3's work has been under three headings: radiation-induced tumours; structure of genome amplifications; and collaborative work with others in the Unit, which is not specifically reported, but includes the important fragile site work lead by the team 1.

The question of identifying **radiation-induced tumours** is important and a long-standing interest of the Unit, related to the links between the Unit and the Radiobiology Department of the CEA, seems to exist. The aim has been to identify characteristics of radiation-induced tumours both as a biological phenomenon and for diagnostic or legal application.

The team 3 has proposed characteristic signatures of radiation-induced tumours and the role of RB1, TP53 and MDM interactions, published in an interesting series of good publications Bastide et al, 2009; Gonin-Laurent et al, 2007; Hadj-Hamou et al, 2011 and Ory et al, 2011.

The second heading is detailed analysis of amplicon structure in gliomas. Following influential work reported in Vogt et al, 2004, the team 3 provided one of very few detailed structural analyses of amplicons and their origin and relationship to double minutes (Gibaud et al, 2010), which has been a milestone in the development of our knowledge of amplicon structure and mechanism that will be widely cited.

Assessment of the team's academic reputation and appeal

As noted above, the work on amplification has achieved international recognition and well be extensively cited.

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

Not applicable

Assessment of the team's organisation and life

Not applicable

Assessment of the team's involvement in training through research

Not applicable as the involvement of the training is done at the level of the overall unit.

Assessment of the five-year plan and strategy

Not applicable. The team disappears in the future project of the laboratory due to the retirement of the team leader.

Conclusion

- Strengths and opportunities:

Not applicable

- Weaknesses and threats:

Not applicable

- Recommendations:

Not applicable

Team 4 : Recombination and genome instability

Name of team leader: Mr Alain NICOLAS

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	1	1	1
N3: Other permanent staff (without research duties)	1	1	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2	2
N6: Other contractual staff (without research duties)	1	1	
TOTAL N1 to N6	6	6	4

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

• Detailed assessments

Assessment of scientific quality and outputs

The team 4 has addressed a number of different aspects of genetic recombination and genome stability using budding yeast as a model system. Much of the work has focused on the manner in which the location and efficiency Spo11-induced double-strand breaks in meiosis are specified. A second aim is to understand the basis of minisatellite instability. A more recently developed aim is to gain insight into the roles of the human BRCA1 by developing assays in yeast. The team has been very productive during the five last years (more than 20 papers have been published by the group leader, some of which are in very high ranking journals).

Part I. Mechanisms, control and biological role of meiotic recombination

Over the past several years, the lab has shown a strong correlation of specific histone modifications and the localization of meiotic DSBs, most notably histone methylation at H3K4. This work has been extended in collaboration with other labs to characterize the role of the COMPASS complex. They showed that tethering Ssp1 subunit to recombinationally cold regions is sufficient to induce DSB formation and that Ssp1 physically interacts with Mer2, which is a component of the differentiated chromosomal axis. Thus, they identified the Spp1 subunit as a link to the Mer2 protein that is required for DSB formation. This work has been published in Science at the very beginning of 2013.

A second approach has been to artificially tether Spo11 or proteins that recruit Spo11 to different sites in the genome – notably "cold spots" – and to compare their consequences. Interestingly, different tetherings lead to different degrees of cis-acting repression of normal hotspot activity. At present these approaches are being translated to study mouse meiosis, although no results have yet been obtained.

Part II. Mechanisms of genetic instability

Work in this area has been another hallmark of the lab.

Mechanisms of minisatellite instability.

The team studied the behaviour of the human CEB1 minisatellite inserted in the yeast genome and especially focused on the biological role of the G-quadruplex (G4) structures. Recent findings that the pif1Δ mutation and G4-quartet binding ligands provoke instability of the human CEB1 and other sequences have led to the demonstration that instability is provoked by replication-induced errors that appear to be linked to G4 formation on the leading strand.

Mutome.

A number of laboratories worldwide are engaged in using NextGen Sequencing to examine the spectrum of mutations, genome wide, caused by various "mutator" mutations both in yeast and in mammalian/human cells. This is clearly a very important effort. One notable observation reported by the team is that some yeast clones exhibited a "cascade" of mutations that may be relevant for the accumulation of mutations during tumorigenesis. Eventually this approach will be extended to human cells.

Part III. Breast Cancer gene predisposition: functional assays for BRCA1 using yeast

Expression of wild-type human BRCA1 in yeast causes slow growth and a mCherry fusion forms an aggregate in the nucleus. The team designed two functional assays in yeast cells to assess the functionality of BRCA1:the SCP (Small Colony Phenotype) and the YLP (Yeast Localization Phenotype) assay. Various pathogenic BRCA1 mutants alter these properties. These assays have been designed to analyse the functionality of BRCA1 variants of unknown significance ("VUS").

Assessment of the team's academic reputation and appeal

It is clear that the team is moving ahead very successfully on several fronts. The PI is regularly invited in both national and international meetings.

The list of collaborators on these projects is impressive and widens the scope of the team's investigations. The team is clearly attractive for high standard students and post-docs.

Foreign professors that have spent a sabbatical stay in the lab or at the Institute Curie have active collaborations with the team.

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

The PI invented patents and contributed to the creation of an innovative start-up in 2010.

Assessment of the team's organisation and life

Not applicable

Assessment of the team's involvement in training through research

Not applicable as the involvement of the training is done at the level of the overall unit.

Assessment of the five-year plan and strategy

Part I. Mechanisms, control and biological role of meiotic recombination

The studies of the COMPASS complex will be pursued using genetics, molecular and cell biology approaches to decipher the precise roles of the interaction between Ssp1 and Mer2 in the initiation of the recombination.

The studies concerning the Spo11 targeted DSB sites in yeast will be extended to additional Spo11 fusions to other transcription factors in order to further interrogate the states of the chromosomal regions with their capacity of DSB formation. The committee believes that it would be of interest to understand better what is happening about meiotic break interference by combining two artificial breaks in a given chromosomal region using the Spo11 fusions already available.

A novel mouse Spo11 fusion has been designed to assess the impact of Spo11 targeted DSB sites in animals.

Another new goal is to compare the profile of meiotic recombination in a highly polymorphic diploid with that obtained if DSBs are initiated meiotically but cells are then returned to vegetative growth after the point of commitment so that repair occurs in more mitotic fashion. The rationale for these experiments is well-established by previous work in other labs. Normally the profile of recombination is obtained by genotyping haploid meiotic segregants. Here, in "return to growth" conditions, the cells will be mosaic diploid colonies.

Part II. Mechanisms of genetic instability

Mechanisms of minisatellite instability.

The lab will pursue the study of molecular mechanisms of G4 and replication-dependent minisatellite instability using ChIP and ChIP Seq to determine how G4 forms during replication.

They also propose to evaluate the pertinence of G4 potential forming sequences identified *in silico* using the *in vivo* assays they developed in yeast. Finally, they want to perform structure/function analyses of G4 by combining biological and chemical approaches in collaboration with two different labs. The idea of modifying minisatellite arrays to learn what are the key instability determinants is very important

Part III. Translational cancer research

A large collection of BRCA1 mutants now classified as "of unknown significance" will be characterized to see if there is a significant distinction between clinically important and neutral mutations in yeast. Thus yeast may be useful to screen mutants for those that correlate with at-risk mutations in humans. The committee believes that it would be important to better understand why overexpressing this human protein in yeast causes a growth defect, and to what extent it is relevant to any aspect of its function in mammals. Similar approaches have been developed with p53 by others, but did not significantly advance research on p53 in mammalian cells.

Early expertise of the team in mastering the technology of NGS allows the lab to collaborate with another team at IC to determine the site of Human Papilloma Virus chromosomal insertions.

Conclusion

● Strengths and opportunities:

- The team is very successful on different topics.

- The team has developed useful tools that make it attractive for collaborations.

- The team has developed fruitful collaborations allowing the questions raised to be extended and increased.

- The team can combine very basic science and translational cancer research.

● Weaknesses and threats:

Two CR1s have already left the group last year, and it seems that the project of the team will probably stop in 2016.

● Recommendations:

This is an excellent high impact team, with a very good scientific production. It has also a good social and economic impact, taking into account the creation of a startup exploiting an in house patent, and, in addition, the implementation of translational projects. This combination is rather rare in such basic science oriented laboratories.

Team 5 : Genetics of Tumor Suppression

Name of team leader: Mr Franck TOLEDO

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	2	2	2
N2: Permanent EPST or EPIC researchers and similar positions			
N3: Other permanent staff (without research duties)	2	2	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)			
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	4	4	2

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

• Detailed assessments

Assessment of scientific quality and outputs

The team is working on the regulation of P53, specially on the generation and analysis of cancer mouse models to improve the understanding of P53 mechanism, in the context of anti-cancer strategy or in the context of basic reseach.

The work's report from 2008 to 2012 is divided in 3 parts.

Part 1 is based on the fact that **the level of P53 expression should be considered in the evaluation of therapeutic anti-cancer strategies**. Indeed, in mouse models, the team has demonstrated that the loss of a single allele of the Mdm4 gene (a major p53 negative regulator) improves survival (in a Rb+/- spontaneous tumor background) but only in a P53 wt background (in the absence of an efficient P53).

The results are convincing in the mouse models presented, but the question is the relevance with the human model, taking into account the fact that the results are depending on the tumor type and as the aim of the work is to improve human therapy. What is the minimum amount of P53 required to target Mdm4 ?

Part 2 is based on a mouse model to **evaluate the role of the P53 C-terminal domain (CTD),** which is poorly understood. The homozygote mice lacking the last 31 residues of this domain are smaller and died 14 to 43 days after birth from bone marrow failure with an increased p53 activity showing that the CTD domain has a negative regulatory role on P53.

The results are nice and raise interesting questions about the mechanism of action of the residues of the CTD domain of P53. Do we have any idea of the status of these 3 residues in human cell lines and on the effect on cell cycle ? It seems that some of these questions will be answered soon as the analysis of these mutant mice are part of the projects of the team.

-**Part 3** is based on the **difference between mouse and human tumorigenesis** when P53 is involved. They take the example of retinoblastoma. Indeed the unique mutation of the RB1 gene leads to retinoblastoma in human but not in mouse, in which it has to be associated with a mutation in p130. The team observed that this difference is due to the fact that P53 transactivates p130 in mouse but not in human.

These results are convincing and nicely explain the difference between mouse models and human based on molecular anaysis of one target of P53, the tumor suppressor Rbl2/p130.

In general, the committee questions the relevance of using mouse in view of improving human cancer therapy, as, from many results, including the group's, mouse is not the most reliable model for p53 induced oncogenesis. However, using mouse to understand p53 mode of action, as in part 2, is certainly of great interest.

The team's record of publications is not among the best of the unit, with only 2 "in house" scientific publications in good but not outstanding journals (PloS Genet and a short communication in Oncogene) and a few reviews including a comment in Nature.

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

Not applicable

Assessment of the team's organisation and life

Not applicable

Assessment of the team's involvement in training through research

Not applicable as the involvement of the training is done at the level of the overall unit.

Assessment of the five-year plan and strategy

The team will continue to focus on P53 by trying to: (1) understand the regulation of the pathway, (2) evaluate anti-cancer strategies and (3) discover new P53 target genes.

1-**Regulation of P53 pathway**:The understanding of the regulation of the pathway will represent the main part of the future work and the team will focus on the analysis of the role of alternative isoforms in the P53 pathway (P53 by itself and Mdm2 and Mdm4 isoforms), always through mouse models.

***The mice p53ΔAS** (deletion of the AS 'Alternative Splicing' exon) is ready and analysis on MEF has already shown a decrease in the capacity to induce apoptosis in irradiated mutant thymocytes and a predisposition to thymic lymphoma.

***The mice p53Δint4** (deletion of the intron containing the internal promoter 2) is ready and preliminary results suggest that the mutants activate the P53 pathway.

These preliminary results are to be confirmed and precisely analysed.

* **Mice mutant Mdm2^{p76},** lack the domain of interaction with P53 (represents one major isoform). The Mdm2 gene encodes a P53 inhibitor that acts as an E3 ubiquitin ligase targeting the degradation of P53. These mice are inducible and are currently mated to express the mutation.

* **Mice mutant Mdm4$^{\Delta_{E6}}$,** lack the exon 6 of Mdm4 wich encodes the other major inhibitor of P53. This shorter isoform is highly expressed in agressive tumors, and conflicting results on its behaviour have been described. These mice are currently mated to obtain homozygous mice.

***The mice p53ΔCTD. :** Further analyses on these mutants are ongoing.

2-**Anticancer strategy based on P53**:

Again the team will create a mouse model of one particular hot-spot mutation : p53Y217C, homologous to the human one, found in about 100 000 cases of worldwide sporadic cancers each year. Structural studies have shown that this mutation destabilized the DNA binding domain of P53 and creates a pocket at the protein's surface that can be targeted by drugs in order to stabilize P53. The work will be done in collaboration with the team who found an effective drug, and the mouse model will be used to test the efficacy of the therapy.

The generation of mouse models is currently on going.

3-**Identification of new P53 target genes**:

The team mentioned that 3 genes have been identified that are regulated by P53 in both human an mice. No more information was provided.

Conclusion

The group has been started 5 years ago only and its main goal is to better understand the P53 pathway, using mainly in vivo mouse models, by generating and crossing genetically modified mice.

- Strengths and opportunities:

The strength of this team is that they use an in vivo integrated model which gives robust results on tumorogenesis. The team is composed of 4 permanent researchers : 1 Professor and 1 MCU, and two engineers. This should be a suffcient task force to allow a scientific production of quantity and quality.

An original and interesting observation was made on p53 CTD and telomeres, and the group is in the proper environment, with team 2 in close vicinity, to get the best out of it.

- Weaknesses and threats:

The committee is concerned with the team's record of publications in the context of this outstanding unit. Presumably the long time required to establish mouse colonies and breeding programmes is partly responsible, as is the involvement of the group leader in University teaching.

The committee is also concerned about the integration of the programme within the Unit, which is considered less convincing than that of other groups

- Recommendations:

The comitee believes that the result on the link between p53 CTD and telomeres should raise the interest of the community. The committee recommends that the group focuses on this part of the project and strengthens its interactions with team 2 in order to explore the p53/telomeres link at the molecular level. The team might also benefit from diversifying its technological approaches beyond the mouse models, as mice do not allow to explore molecular mechanisms. The team might also consider extending collaborations within the immediate Curie environment interested in oncogenes and tumor suppressors.

Team 6 : Non Coding RNA, epigenetics and genome fluidity

Name of team leader: Mr Antonin MORILLON

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	2	2	1
N3: Other permanent staff (without research duties)	1	1	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1	1
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	5	5	3

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	1	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

The group was recruited to the Curie Institute in 2009. The work has been focused on gene regulation and in particular on the characterization of the role of long non-coding RNAs (lncRNAs). Before moving to Curie, the group characterized the role of ncRNAs on Ty expression showing that Ty silencing has similarities to telomeric position effects. They showed that antisense Ty RNAs control Ty expression via a process that involves chromatin methylation such as methylation by Set1. They also showed that H3K4me2/3 deposition into promoters was initiated by ncRNAs suggesting that promoter fidelity of genes is controlled by CUTs. These two studies were published in Genes Dev. and EMBO J. in 2008 and 2009.

At the Curie Institute, the group has focused on the analysis of ncRNAs specifically sensitive to the Xrn1 ribonuclease. Using yeast xrn1- mutants and RNAseq they have identified a novel class of ncRNAs termed XUTs. They have shown that XUTs maintain gene silencing only when Set1 is active confirming the role of ncRNAs on gene silencing via histone modifications. This work was published in Nature. In relation to all this work the team has developed an apparently high efficient method to prepare libraries for RNA-seq based on a Zn treatment that is submitted for publication.

Assessment of the team's academic reputation and appeal

The production of the group is highly significant and influential. This recent Nature paper has been a strong achievement with the new concept of XUTs The quality and potential of this work has been supported by an EMBO YIP nomination of the PI and an ERC starting grant for the 2010-2014 period. Previously they have made important contributions in EMBO J and Genes Dev. Ther are active collaborations via some of the components of the group with the a laboratory at Oxford university (UK). The group consists of 7 people, including a pretty active DR1 researcher, 1 postdoc and two PhD students, in addition to technicians. It seems that some of these positions need to be stabilized. The relevance of the work is also supported by the participation of the PI as an invited speaker at international meetings such as FEBS workshop in Denmark 2012, Jacques Monod conference in France 2012, a symposium in Taiwan 2011, in an ARN meeting in Dourdan 2010. This group is outstanding.

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

Not applicable

Assessment of the team's organisation and life

Not applicable

Assessment of the team's involvement in training through research

Not applicable as the involvement of the training is done at the level of the overall unit.

Assessment of the five-year plan and strategy

The future research plans are focused on three main points. In the first one, the group will try to characterize the mechanisms of XUT-mediated regulation in yeast. For this, the group will use genome-wide approaches in different yeast species harboring or not the siRNA system of gene silencing in a collaborative effort with other groups outside the Curie Institute. They expect that they will be able to identify a regulatory role of XUT by studying the differences in gene expression and XUT pattern in these strains. From a functional viewpoint they will express AGO and DICER from *Drosophila* in *S. cerevisiae* in order to test whether it has the capability of using XUT as a regulator molecule via siRNA machinery as the other yeast species, in the case the hypothesis is correct. Also following their previous work showing that histone methylation and acetylation controlled by Set1 and HDAC are involved in gene silencing by cryptic antisense ncRNAs, they will try to determine whether HDACs are involved in XUT-mediated silencing. At this point they have found that Hda1 has an histone-independent role in transcription elongation that they are trying to decipher. Finally, by using oligonucleotides with bases modified with the Locked Nucleic Acid (LNA) system and biotin they plan to identify proteins binding to XUT RNAs, to explore the functional role of these proteins. At this point they have been able to identify the Rpa1 silencing proteins, typically found at telomeres.

The projects are excellently planned, new and really promising, which will offer them plenty of options to follow up in the future and to establish collaborations. They may, in the future, want to give priorities to some of the lines they are opening now, if all of them are fruitful.

Conclusion

- Strengths and opportunities:

Outstanding work, excellently focused, opened to incorporate novel technologies, with strong involvement in bioinformatics. They have very clear ideas on what research lines to pursue and the way to follow.

- Weaknesses and threats:

No obvious weaknesses

- Recommendations:

The group should have all the support to continue with his work in the best of conditions. They just need to take the right decision on focusing appropriately the research lines after they move forward on the different functional options in which XUTs may be involved.

5 • Conduct of the visit

Visit dates:

Start: 15 January 2013 9AM

End: 16 January 2013 4PM

Visit site(s): Institue Curie (Batiment Biologie du Développement)

Institution: Institue Curie

Address: 26, rue d'Ulm, 75248 Paris Cedex 05

Conduct or programme of visit:

Day one – 15th January 2013

9:00 Welcome (closed-door) Visiting committee with the AERES Scientific advisor

9:15 ***Jacques HAIECH***: the role and procedures of AERES

9:30 Presentation by the **Directors (present and proposed) of the Unit**
(15'+15' presentation, 15' discussion): Past activities and project

10:15 *Coffee break*

10:45 **Team 1 - Functional organization and plasticity of mammalian genomes**
(20' Talk + 15' discussion)
Michelle DEBATISSE

11:20 **Team 2 – Telomeres and Cancer**
(20' Talk + 15' discussion)
Arturo LONDOÑO-VALLEJO

12:00 *Lunch*

14:00 **Team 4 – Recombination and genome instability**
(20' Talk + 15' discussion)
Alain NICOLAS

14:35 **Team 5 – Genetics of Tumor suppression**
(20' Talk + 15' discussion)
Franck TOLEDO

15:10 **Team 6 – Non Coding RNA, epigenetics and genome fluidity**
(20' Talk + 15' discussion)
Antonin MORILLON

15:45 *Coffee break*

16:15 Debriefing on the team presentations + Private discussions with individual team leaders

Day two - 16th January 2013

8:45	**Parallel meetings with personnel:**
	Discussions with engineers, technicians, administrative Discussions with staff scientists Discussions with students and post-docs
9:30	Discussion with the head of the Unit
	10:00 *Coffee break*
10:30	Discussion with the representatives of the managing bodies
11:15	**Private meeting of the visiting committee (in presence of the AERES scientific advisor)**
16:00	End of the visit

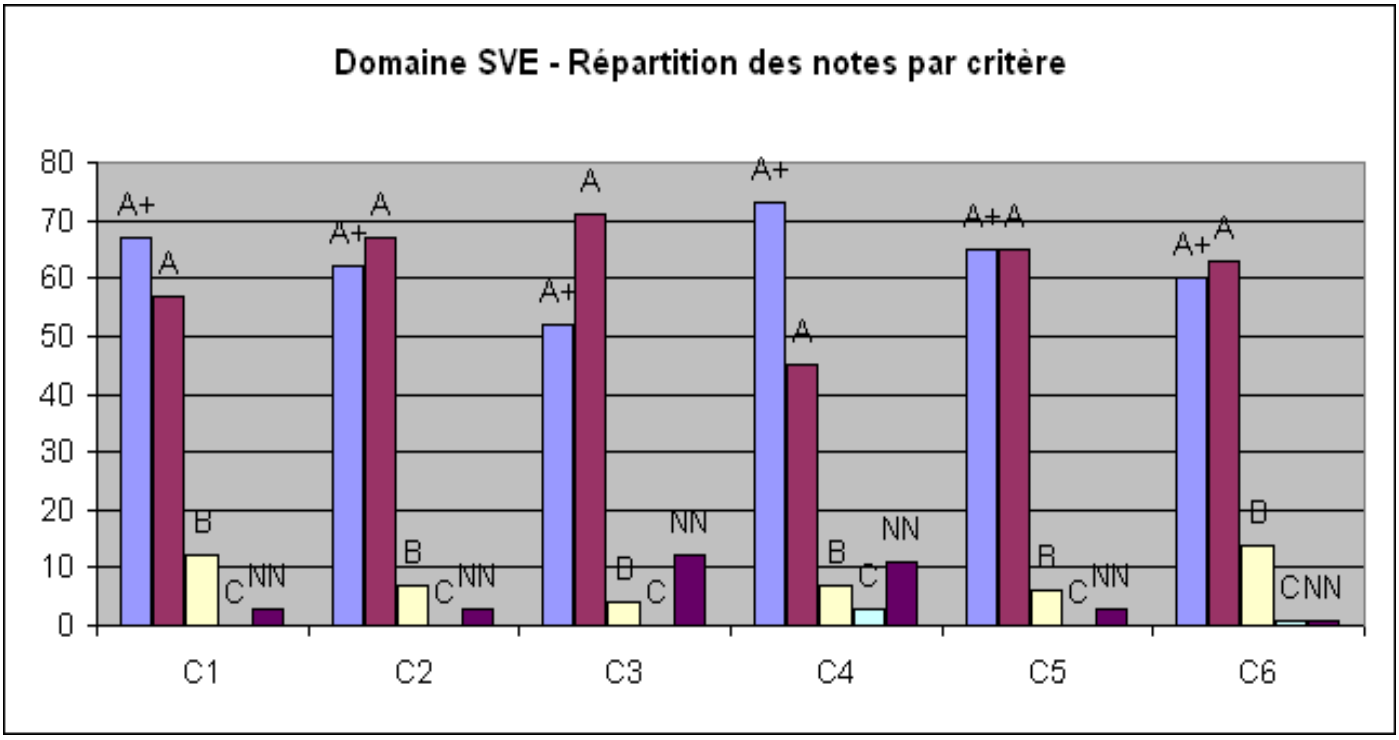
6 • Statistics by field: SVE au 10/06/2013

Notes

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

Pourcentages

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%



7 • Supervising bodies' general comments

CENTRE DE RECHERCHE

institutCurie
Ensemble, prenons le cancer de vitesse.

AERES
Section des Unités
20, rue Vivienne
75002 PARIS

Paris, le 18 avril 2013

Concerne : Rapport : S2PUR140006166 « Dynamique de l'information génétique : Bases fondamentales et cancer » 0753172R
Unité IC/CNRS UMR3244/UPMC : Directeur pressenti : Arturo Londono-Vallejo

Chers Collègues,

En tant qu'organisme hébergeur et déposant unique des rapports des unités de recherche du site de Paris de l'Institut Curie – Vague D, je vous informe avoir bien reçu en date du 2 Avril dernier, le rapport d'évaluation de l'AERES sur l'unité IC/CNRS UMR 3244/UPMC.

J'ai lu ce document avec attention et je tiens à saluer le travail rigoureux du comité, ses commentaires enthousiastes par rapport aux travaux de recherche de cette unité ainsi que sa reconnaissance du grand effort effectué dans des activités d'enseignement.

Afin d'assurer le succès continu de cette unité, je note bien les recommandations du comité pour appuyer ce plan en tenant compte de l'évolution de cette unité et tous les efforts seront faits en coordination avec les tutelles : l'Institut Curie, le CNRS et l'Université Marie-Curie (Paris 6) pour assurer les soutiens nécessaires.

Je tiens à exprimer tous mes remerciements aux membres du comité d'évaluation pour leurs commentaires et recommandations très pertinents qui sont basés sur un travail d'analyse approfondie. Je remercie également la Présidente, le délégué de l'AERES et de tous les membres du comité de visite qui soutiennent la mise en oeuvre de l'ensemble de cette évaluation.

Je vous prie d'accepter, Chers Collègues, mes plus cordiales salutations.

Daniel LOUVARD
Directeur de la Section de Recherche
INSTITUT CURIE

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