Stabilité génétique et oncogénèse

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Genetic Stability and Oncogenesis

Under the supervision of the following institutions and research bodies:

Université Paris Sud

Centre National de la Recherche Scientifique - CNRS

December 2013

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

Department for the evaluation of research units

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

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

On behalf of the expert committee,

- Mr. Vincent GÉLI, chair of the committee

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

Evaluation report

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

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

Unit name:	Genetic Stability and Oncogenesis
Unit acronym:	
Label requested:	UMR
Present no.:	UMR 8200
Name of Director (2013-2014):	Ms Patricia KANNOUCHE
Name of Project Leader (2015-2019):	Ms Patricia KANNOUCHE

Expert committee members

Chair:

Mr Vincent GELI, Université d'Aix-Marseille

Experts:

Mr Rodrigo BERMEJO, Institute for Functional Biology and Genomics, Salamanca, Spain

Mr Frédéric COIN, Université de Strasbourg

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

Mr Michael LISBY, University of Copenhagen, Denmark

Mr Jacques ORGIAZZI, Université Lyon 1

Mr Jean-Marc REICHART, Université de Strasbourg (representative of the CNU)

Scientific delegate representing the AERES:

Mr Jean ROSENBAUM

Representatives of the unit's supervising institutions and bodies:

Mr Christian AUCLAIR (director of Doctoral School n°418)

Mr Etienne AUGE, Université Paris Sud

Mr Domenico LIBRI, CNRS

1 • Introduction

History and geographical location of the unit

The "Genetic Stability and Oncogenesis Unit" (UMR8200) is located on the Gustave Roussy Cancer Campus at Villejuif. The unit belongs to the IFR 54, an Integrated Research Cancer Institute in Villejuif (IRCIV). The UMR 8200 includes 55 people including 25 permanent research staff (1 DRCE, 5DR, 7 CR, 2PUPH, 1 MCU, 1 PU emeritus and 8 ITA). The UMR 8200 is affiliated to the CNRS, Gustave Roussy Institute and the University of Paris Sud. The unit brings an added value having the DNA Repair expertise in the Institute. In 2010 the unit hosted 5 groups working on closely related topics connected to genetic instability. Team 3 has joined the unit in 2012 and an ATIP/AVENIR team will join the unit in 2014. For the next contract (2015-2019), the research unit will be formed by 5 teams. Two teams result from the merging of pre-existing teams. The new teams have been evaluated by the AERES committee except the ATIP/AVENIR team.

The UMR 8200 objectives are to generate scientific progress in the mechanistic understanding of genome stability at multi-scale levels (molecular level, cell, organisms). The projects of the unit are remarkably focused on the mechanisms that govern genetic stability with a particular emphasis on DNA repair, DNA replication, mutagenesis, Homologous Recombination, and oxidative stress with outputs in rare diseases, diversification in B lymphocyte, and cancer. These objectives are supported by a scientific policy that entails independent research groups that constitute scientific units, transparent and collegial governance and shared resources.

The location of the UMR 8200 facilitates collaborations with the clinic departments of the IGR and translation of their fundamental knowledge in terms of clinics. This is demonstrated by the participation of the teams of the unit to the SIRIC (Integrated Cancer Research Sites) programme, the leader of Team 2 being the coordinator of the DNA repair axis.

Management team

The present director of the UMR 8200 is a world-recognized scientist in the field of translesion synthesis (TLS). She has a preeminent role in synergizing the activities of the teams and promoting the cross-fertilization between team activities and the cancer translational research. The management of the UMR 8200 relies on 2 main bodies. The steering committee is composed of the director and one or two members of the teams. The steering committee deals with scientific and organizational strategy and manages most of the decisions related to the scientific life of the Unit including recruitment of new teams, allocation of financial support and space, and day-to-day running of the Unit. The Laboratory Council (Conseil de Laboratoire) represents the unit with the appropriate proportion of technical staff, post-docs and PhD students. The CL meets twice a year and is informed about information and decisions. The CL gives advice on internal matters, equipment maintenance responsibilities, ITA promotion politics and safety rules. The Unit has no Scientific Advisory Board (SAB). The management of the unit appears satisfactory. The meeting with the different categories of staff revealed a consensual agreement about the management of the Unit. A particular attention should be given to the career development of the ITA, overall because they have overwork due the very low ratio of ITA in the Unit.

AERES nomenclature

SVE1_LS2; SVE1_LS1; SVE1_LS4; SVE1_LS6

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	4	4
N2: Permanent researchers from Institutions and similar positions	11	10
N3: Other permanent staff (without research duties)	9	6
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	2
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	9	8
N6: Other contractual staff (without research duties)	2	4
TOTAL N1 to N6	**36**	**34**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	13	
Theses defended	18	
Postdoctoral students having spent at least 12 months in the unit*	16	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	11	12

2 • Assessment of the unit

Strengths and opportunities related to the context

Over the past few years the UMR 8200 has solidified its position with several highlight in the DNA repair field and PIs being recognized as leaders in their related respective field of research. The overall scientific level of this Unit is very good with many publications in high impact journals. The evaluation committee encourages all the teams of the UMR 8200 not only to maintain this level but to increase excellence and ambition even further by consolidating the internal synergy between the teams and develop international collaborations. The recruitment of an excellent ATIP/AVENIR team goes in this direction.

The Unit project is a synergistic project covering scientific goals focused on genetic stability and mobilizing a broad range of experimental methods and techniques. Remarkably, the unit project allows scientists of the different teams to combine their know-how and complementary expertise in cell biology, genetics, biochemistry and molecular biology in an effective manner.

The committee was also impressed about the interactions with teams involved in cancer diagnosis and treatments. These kinds of interactions are quite unique in France and represent a model for the evolution of cancer research. The financial situation of the UMR 8200 is good with an overall budject of more than 5 million euros (excluding salaries from permanent staff). The situation is less clear about the sources to improve or even maintain the scientific infrastructure. The committee recommends to further support the UMR 8200 infrastructure.

Weaknesses and threats related to the context

The team has a huge deficit in ITA staff. This Unit has been 15 years without a single recruitment of ITA, something that is not normal specially for a Unit with such scientific quality. Moreover, the unit has lost two positions due to internal mobilities (NOEMI) and 4 positions due to retirements

The UMR 8200 teams have the scientific quality and recognition to participate in European and international consortia. Some team leaders could even lead such activities.

It was not completely clear how the teams of the UMR 8200 access common services and facilities, including cutting edge technological platforms.

Recommendations

The team leaders of the UMR 8200 in close interaction with the experienced PIs, should carry on to develop a long-term vision about the added value of having their scientific expertise at the institute.

The Unit should increase its critical mass in a near future with the recruitment of at least 1 team to further increase the synergies that are already very efficiently exploited by the teams. A team with experience in Epigenetics would be an added value to the unit.

The Committee approves the merger of units that have been proposed for the next contract providing that it will not be just juxtaposing activities but rather a synergistic work on common scientific projects. The committee recommends that the newly merged teams share open space, scientific goals and animation, and financial support.

The committee encourages the UMR 8200 to participate in international activities. CR scientist from team 2 is encouraged to apply for an ERC for young investigators.

Although the research projects of the Unit should be kept dedicated to fundamental aspects, the Committee encourages the teams to answer to SIRIC calls.

A website for the team should be established in English to promote international recruitment.

3 • Detailed assessments

Assessment of scientific quality and outputs

The laboratory has a world-recognized expertise in several aspects related to genome stability. Assessment of the scientific production of the laboratory shows a total of 137 publications in peer-reviewed scientific journals over the last 5 years, excluding clinical publications with more than 70 articles over the period. The average impact of the publications is very good since 30% of the papers have an IF between 15 and 7. They have some outstanding contributions in which the members of the Unit appear as last author that have been published in high-ranking scientific journals such as Nat Cell Biol, Mol Cell, PNAS, Cell reports. About half of all research articles are collaborative, and 13% of them include members from different units in Gustave Roussy, demonstrating scientific interactions in the Institute. Finally, results have been presented as posters or oral communications at the main national and international scientific meetings in the fields of DNA repair, DNA damage response, genome instability, reactive oxygen species (ROS) and thyroid tumorigenesis and Ig gene diversification in B lymphocyte. In total, members of the unit have been invited in 60 meetings between 1st January 2010 and mid-2013 with 64% in international meetings.

Assessment of the unit's academic reputation and appeal

The academic reputation and visibility of the laboratory is underscored by some outstanding contributions with a fraction (3.5%) of the papers having an IF>15, the large number of invitations of several members of the lab to act as speakers at national and international meetings, and the fact that several lab members received different prizes (Prize LNCC, Prize Dandrimont-Bénicourt 2013, Prize Lavrentiev 2012). Moreover, recognized scientists have been recently recruited or joined the lab including one ATIP/Avenir team that will start in the unit in April 2014, further demonstrating the excellent unit's academic reputation. Finally, several members of the unit take an active part in the scientific expertise for funding organizations (INCA, ARC, LNNC).

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

There is a significant impact of work done at the Unit in particular on the health sector. The UMR8200 takes part in the recently funded “Integrated Cancer Center“ (SIRIC) that has been set-up to stimulate integrated research from basic to applied science and collaboration between clinicians and academic researchers. In this program, the DNA Repair axis is coordinated by the leader of Team 2. DNA Repair has become one of the main research axes at Gustave Roussy. The development of predictive tests monitoring DNA Replication and repair will permit individualized treatment options of DNA-damaging drugs and radiotherapy. Such tests may be patentable and could be integrated in clinical trials based on pre-selection of patients.

In addition, the director of the unit is a member of the steering committee of the IRCIV as well as a member of Scientific Policy Committee at IGR that discusses the main scientific and clinical orientations of the Research in the Institute.

Assessment of the unit's organisation and life

The decision-making structures of the unit are well-organized, and each team is working in an autonomous manner. There is a strong cohesion between people working within the unit. Concerning financial aspects the Unit is in a rather favorable situation due to the efficient recruitment of grants. However, resources are limited to further improve the scientific infrastructure of the Unit.

Assessment of the unit's involvement in training through research

There is a strong and supportive relationship between PhD students, postdocs and senior researchers in the unit. Weekly lab meetings are organized so that the monitoring of the research activities of students/postdocs is efficient. Additionally, students/postdocs are encouraged to attend national and international meetings where they can present their work to the scientific community.

In addition to the teaching activities displayed by Professors/Assistant-Professors (840 h), 6 researchers of the unit participate in teaching (190 h/year) at the major universities of Ile-de-France, Pasteur Institute and the Ecole Normale Supérieure de Cachan. Of note 80 hours per year are delivered in Universities of the Republic of Kazakhstan by Team 4.

Assessment of the strategy and the five-year plan

The committee very strongly supports the five-year research plan of the unit that consists in tackling different aspects of genome integrity maintenance from fundamental research to clinic translational and biotechnological developments, in a continuum of biological models from yeast (ATIP Team) to mammalian cells and including patients. The unit is currently implementing the human and organisational resources to succeed in this ambitious challenge. It will be important to maintain research excellence to promote the international visibility of the unit and further develop the links between the researchers of the unit with the international cutting edge research performed in the field. The committee encourages the recruitment of an epigenetic group to include the epigenome maintenance in the central topics of the unit. Finally, the committee commends the efforts of the director to stimulate the links between clinicians and the academic researchers working in the Unit.

4 • Team-by-team analysis

Team 1 : TLS Polymerases and Cancer

Name of team leader: Ms Patricia KANNOUCHE

Workforce : Fusion between Ms Patricia KANNOUCHE's team and Mr S. AOUFOUCHI's team for the next contract

Team workforce	Number as at 30/06/2013		Number as at 01/01/2015
	Former PK Team	Former SA Team	
N1: Permanent professors and similar positions			1
N2: Permanent EPST or EPIC researchers and similar positions	2	1	2
N3: Other permanent staff (without research duties)	1	1	2
N4: Other professors (PREM, ECC, etc.)			1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1		1
N6: Other contractual staff (without research duties)			2
TOTAL N1 to N6	**4**	**2**	**9**

Team workforce	Number as at 30/06/2013		Number as at 01/01/2015
	Former PK Team	Former SA Team	
Doctoral students	2	1	
Theses defended	3	1	
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	2

• Detailed assessments

Assessment of scientific quality and outputs

The Kannouche team's research program builds mainly on the team leader's expertise on Translesion Synthesis (TLS) DNA polymerases. Recruitment of TLS polymerases to replication forks as a bulky DNA lesion by-pass mechanism and TLS implications in genome stability maintenance are relevant and highly competitive topics.

The team's research has been focused on analyzing the regulation of TLS polymerases (pol eta and pol iota), as well as on the mechanistic characterization of the TLS process and its impact on protecting genetic stability in higher eukaryotic cells in response to oxidative damage. The team provided insight into the function and fine regulation of the TLS polymerase pol eta, revealing its importance for the functionality of replication forks facing ultraviolet (UV) light-induced DNA lesions and uncovering the role of pol eta's ubiquitin-binding (UBZ) and PCNA interacting peptide (PIP) domains in controlling its association to replication forks. The team also analyzed Fbh1 helicase function in favouring TLS by suppressing Homologous Recombination (HR) via its recruitment to replication factories and subsequent degradation, in a mechanism dependent on Fbh1-PCNA interaction. The team uncovered a "non-canonical" function of pol eta in response to oxidative damage, by which it is recruited to oxidative lesions independently of DNA replication and through the action of the Msh2-Msh6 Base Excision Repair (BER) factors. Lastly, the team reported a novel role for the pol iota TLS polymerase in the repair of oxidative lesions.

The topics engaged by the team are original and have provided a significant advancement in the understanding of important aspects of TLS polymerases function and novel TLS mechanisms suppressing genetic instability. The publication record of the team for this period is very good, with papers published in prestigious journals like Molecular Cell, EMBO Journal, Nucleic Acids Research and Human Molecular Genetics, which received a significant number of citations.

The Genome Plasticity and B cells team experienced a change of leadership in 2010 in which a new researcher took charge replacing the previous leader. The team's research has focused on the DNA repair mechanisms generating immunoglobulin (Ig) gene diversity. This topic is relevant and has potential implications for human health.

A first interest of the team is the regulation of single-stranded-DNA-specific cytidine deaminase (AID), a factor essential for priming somatic hypermutation (SMH) and class switch recombination (CSR) at Ig genes. The unit reported the importance of subcellular distribution on AID stability and how it affects its degradation by the proteasome. A second research interest has been the role of TLS polymerases in somatic hypermutation. The team contributed to show that the TLS polymerase kappa can exert a backup role in this process by substituting polymerase eta when the latter is absent. Since its change in leadership the team has focused on studying a novel role of the cohesin complex subunit RAD21 in CSR, the impact of limiting polymerase eta availability on genomic stability and the role of the Fanconi Anemia pathway on CSR and SHM.

The topics tackled by the team are original and have the potential to contribute to advancing the current understanding of important aspects of human Ig genes diversity generation. The publication record of the team for this period is fair, likely limited by the reshaping of the team and the establishment of new research lines. The team has published in good journals like J Exp Research, J Clin Investigation, J Immunol, Curr Opin Immunol and DNA repair both primary and collaborative papers, which have overall received a significant number of citations. Work from the newly established research lines has been submitted or is in preparation for submission, but has not been published at the date of the evaluation.

Assessment of the unit's academic reputation and appeal

The TLS polymerases and Cancer team's reputation is very good, as judged by the quality of the journals in which its research was published and by the number of citations. The team has a high involvement in national collaborative projects, though participation in international projects is not described. The team leader has been invited speaker in several relevant meetings such as the Gordon Conference on Mammalian DNA repair 2013 and has received the *Dandrimont-Bénicourt* prize in 2013. The team leader acts as *ad hoc* reviewer for prestigious journals and belongs to the INAC and ERC (external) reviewing boards. Internationalization in terms of recruitment of foreign students is in place.

The Genome plasticity and B cells team's reputation is fair, based on the quality of the journals in which its research was published and the number of citations received. The team leader has been invited speaker in

international meetings such as the Workshop on AID biology in 2013 and the 26th annual symposium of the Protein Society in 2012. The team leader acts as reviewer of scientific papers and has participated in the organization of meetings.

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

TLS polymerases and Cancer team: Interaction with the social, economic and cultural environment is good, and has been established through the participation of the team leader (Ms Patricia KANNOUCHE) in consulting for a private laboratory, radio interviewing and participation in invited seminars at a company.

Genome plasticity and B cells team: Interaction with the social, economic and cultural environment was established through the participation of the team leader in the organization of scientific workshops in high schools and universities and by serving as consultant for the media.

Assessment of the unit's organisation and life

Judging from the unit's report and the site visit the team is very well organized with a precise scientific objective and clearly defined roles within the unit. The accessibility of the teams to the pooled resources, the scientific coordination structures and the incentivising of team emergence are coherent and well organized.

The teams are very well integrated at *Institut Gustave Roussy* and within the unit, and hold several collaborations at a national and international level.

Assessment of the unit's involvement in training through research

TLS polymerases and Cancer team: During this period the team has a good training record including 5 PhD students, 6 Master students and 9 undergraduate students. Of these, 2 PhD students have contributed as main author and collaborative publications, indicative of a good training, and have moved to appropriate postdoctoral positions. The team leader took part in teaching in French universities and has been involved in thesis evaluation committees, attaining an adequate outreach at regional and national level.

Genome plasticity and B cells team: During this period the team has a fair training record including a PhD student, as well as master students and undergraduate students. The PhD student is currently in the 3rd year and has not yet contributed with publications. The team members took part in teaching in French and UK universities.

Assessment of the strategy and the five-year plan

TLS polymerases and Cancer team: The future research plan and strategy are consistent with the team expertise and suppose a coherent expansion towards open questions in the function of TLS mechanisms.

A research line aims at exploring the molecular mechanisms mediating UV-lesion bypass in human cells. The team will analyse the role of pol eta SUMOylation in its stability/processivity, as well as the role of SUMO conjugating enzymes potentially acting on pol eta and Rad18. The function of TLS factors in promoting lesion by-pass directly at replication forks will also be explored in an approach employing different techniques such as electron microscopy, iPOND and proteomic searches. Part of this research relies on collaborations with other groups and on methodologies recently implemented by the team. A second research line aims at exploring a possible role of TLS factors in promoting heterochromatic regions replication and will explore the importance of such mechanism by addressing the impact of Pol zeta defects on fork progression and on the maintenance of the epigenetic landscape.

Additional research lines will be carried out by an emeritus professor within the TLS polymerase group headed by Ms Patricia KANNOUCHE. Two research lines will be carried out in collaboration with the PK and Genome Plasticity groups, as a continuation of previous work. The objectives and methodological strategy to develop these research lines are not stated in the report. In addition, an emeritus professor in the team will carry out studies on the DNA repair-deficient syndromes xeroderma pigmentosum (XP) and Cockayne syndrome (CS). A link between historic slavery process on African populations and the propagation of XP-causing mutations will be explored and the identity of a putative mutation causing myeolodisplasy in XP patients will be sought through genetic analysis of different patients and cohorts. Research related to a mitochrondrial alterations in CS patients will be carried out, though objectives and strategies are not described.

The proposed research strategy is in general original and supported by strong preliminary evidence, thus reducing the inherent risk of exploring novel hypotheses. The proposed research is credible and reflects the team's capacity to adapt to novel findings and ideas emerging in the research field. The proposed research strategy is expected to maintain the team's good productivity.

Genome plasticity and B cells team: There are two main lines in the future research plan and strategy. The first one emanates from the current team's research and aims at identifying factors and/or post-translational modifications driving mismatch repair (MMR) factors to mediate somatic hypermutation (SHM) at Ig V genes. The second one aims at exploring the interplay between AID and TET2 oxygenase in a putative epigenetic pathway suppressing haemopoietic malignancies. This strategy is original and has the potential to render interesting insights into the analysed processes. The proposed research is consistent with the team's experience and is overall credible. The group's future reputation will depend on the quality of the scientific output of these research lines, as well as on that of the work carried out since 2010.

Overall, the Ms Patricia KANNOUCHE's team proposed research reflects the team's capacity to adapt to novel findings and ideas emerging in the research field. The involvement of non-academic partners is not explicit in the research plan. The SWOT analysis is realistic and provides an accurate assessment for strategic decisions regarding future research directions. In general the five-year research plan is feasible and likely to contribute with important findings regarding TLS-related mechanisms preventing genetic instability.

Conclusion

- **Strengths and opportunities:**

The team has displayed a very good research record and presents very interesting future research prospects. The unit organization and researchers training are excellent. The research strategy is coherent. In most cases supported by preliminary evidence and promising. The implementation of new methodologies and the rearrangement of the team members are expected to enhance the competitiveness of the research team.

- **Weaknesses and threats:**

No major weaknesses are apparent.

- **Recommendations:**

The internationalization of the team by participation in collaborative networks or by recruiting foreign postdoctoral research would boost the team's reputation.

Team 2 : FANC/BRCA Pathways and Cancers

Name of team leader: Mr Filippo ROSSELLI

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	2	1
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)	2	1
N4: Other professors (PREM, ECC, etc.)		1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	2
N6: Other contractual staff (without research duties)	1	1
TOTAL N1 to N6	**11**	**9**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	6	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	4	4

• Detailed assessments

Assessment of scientific quality and outputs

This team is led by Mr Filippo ROSSELLI but contains two scientists with Emeritus who are still scientifically active and published very good papers in the last years. The focus of the team is consequently diverse, each exPI bringing unique expertise in the final pool (i.e. Homologous recombination and Nucleotide excision repair). However the main topic stays the topic of the PI, Mr Filippo ROSSELLI, who is an expert in the FANC/BRCA pathway with many recent achievements in excellent journals. Recently, the group has reported the involvement of FANC in preventing the segregation of defective chromosome, in collaboration with the Bloom protein. They also discovered that the FANC pathway was activated after exposure to UVC. This team is not only performing fundamental science but also tries to use its knowledge in DNA repair to address questions about SNP in DNA repair genes and risk of cancer that may be important in the future to predict cancer outcome. For such projects they use their location a the IGR to interact with Physicians and recolt tumour samples.

The publication record of the lab is excellent, with two papers published in Nature Cell biology and one in Molecular Cell. The PIs also published many papers in the last years as co-authors in collaboration with excellent teams (see below).

Assessment of the unit's academic reputation and appeal

The team's reputation is excellent. Their work is published in very good journals such as Nature Cell Biology or Molecular Cell. Members of the team include highly cited scientists who are regularly invited to conferences. Altogether, the 3 PI were invited to 43 international and national meetings. The team has a high involvement in national collaborative projects.

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

An expert in nucleotide excision repair in the team speaks regularly in media to explain the disease harbored by the so called « children of the moon ». He is recognized as the French expert for these disorders. He participated to several radio/TV programs. Mr Filippo ROSSELLI is a member of the scientific board of the Ligue Nationale contre le Cancer. Also, Mr Filippo ROSSELLI and his team members participate to the annual meeting of the French XP and FA parents association.

Assessment of the unit's organisation and life

The team is well organized with weekly lab meetings and seminars and fruitful interactions with other groups within the unit as evidenced by joint publications. The students and postdocs of the group expressed a high degree of satisfaction and common interest in the social well-being of the group.

Assessment of the unit's involvement in training through research

The team currently has three graduate student and two postdocs.

Assessment of the strategy and the five-year plan

Due to the departure of the emeritus it seems that the projects of the lab will be focused only on the FANC pathway as a direct link with what the team has done these last years. Consequently, the proposed research strategy is in general supported by strong published work, thus reducing the inherent risk of exploring novel hypotheses. The proposed research is credible and reflects the team’s capacity to adapt to novel findings and ideas emerging in the research field. The proposed research strategy is expected to maintain the team’s good productivity, with respect to the “threats” described below. Questions remain about the desire of the unit to create a team with one CR from Rosselli lab. If this lab looses the two emeritus and the CR, it is likely that they will not be able to compete at the international level.

Conclusion

- **Strengths and opportunities:**

Very good record and equally good prospects. The research program is logical and appealing. The future directions are straightforward and promising.

- **Weaknesses and threats:**

Possibility to loose the CR who did the two last big papers of the lab as well as the two recognized Emeritus of the group.

- **Recommendations:**

The impact of the creation of a new team with the CR as PI should be considered relatively to the consequence for the Rosselli team. The CR is in an excellent position to apply for an ERC starting grant.

Team 3 : Recombination/Repair and Cancer

Name of team leader : Mr Bernard LOPEZ

Workforce : Fusion between Mr Bernard LOPEZ's team and Mr C. DUPUY's team for the next contract

Team workforce	Number as at 30/06/2013		Number as at 01/01/2015
	Former BL Team	Former CD Team	
N1: Permanent professors and similar positions		2	2
N2: Permanent EPST or EPIC researchers and similar positions	2	1	3
N3: Other permanent staff (without research duties)		1	
N4: Other professors (PREM, ECC, etc.)		1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2	3
N6: Other contractual staff (without research duties)	1		1
TOTAL N1 to N6	**5**	**7**	**10**

Team workforce	Number as at 30/06/2013		Number as at 01/01/2015
	Former BL Team	Former CD Team	
Doctoral students	1	3	
Theses defended	2	2	
Postdoctoral students having spent at least 12 months in the unit	2	4	
Number of Research Supervisor Qualifications (HDR) taken			
Qualified research supervisors (with an HDR) or similar positions	1	3	4

• Detailed assessments

Assessment of scientific quality and outputs

Mr Bernard LOPEZ (BL) joined the UMR8200 unit in 2012. The primary scientific focus of the team is the regulation and coordination of homologous recombination with DNA replication, end-joining pathways (NHEJ and A-EJ) and mitosis. The team has recently been joined by experts to investigate endogenous sources of DNA replication stress such as reactive oxygen species (ROS) and their implications for radiocarcinogenesis and thyroid cancer.

BL and his team members are internationally recognized for their important contributions to our understanding of the choice of repair pathway for DNA double-strand breaks and the contribution from DNA repair factors such as MRE11, KU80, XRCC4, BRCA1, CtIP, RAD51, TdT and BLM. For example, a recent high-profile paper in Nature Structural and Molecular Biology demonstrated the role of the MRE11 nuclease in alternative NHEJ (presently 128 citations). Several regulatory mechanisms have been elucidated in the reporting period ; most importantly those of AKT1 and Bcl-2, which were shown to inhibit homologous recombination by sequestering BRCA1 and RAD51 in the cytoplasm. Another important finding from BL's lab is the demonstration that homologous recombination is required during unchallenged DNA replication. The members of the 'Reactive oxygen species and Radiocarcinogenesis' team which joins the team are internationally recognized for their long-lasting, innovative and knowledgeable expertise in the identification and characterization of NADPH oxidases and the interactions of oxidative stress with genomic deregulation and carcinogenesis, particularly radiocarcinogenesis, in the thyroid cell/tissue model. The team has also made the important finding that the increased ROS observed after radiotherapy persists for much longer (days) than can be explained by a direct consequence of ionizing radiation.

BL has engaged in several fruitful national and international collaborations e.g. to demonstrate the importance of nucleoporin 153 in DNA double-strand break repair.

The team is exceptionally well balanced between basic and translational research with close ties to clinicians. The strength in this area is supported by access to patients, and tissue samples there from, with various types/stages of thyroid cancer for which IGR is one of the preeminent referral centers in Europe.

The publication record of the lab is outstanding, with many papers in leading journals like Molecular Cell, Oncogene, Cancer Research, Nature Structural and Molecular Biology, and New England Journal of Medicine.

Assessment of the unit's academic reputation and appeal

The team's reputation is excellent. Their work is published in high-impact international journals and frequently cited. BL has many strong collaborators. He coordinates several collaborative research projects and networks and both he and his senior team members are frequently invited to meetings and for individual seminars. He is very well known and highly respected in the DNA repair community.

BL has served on many national and international scientific advisory boards and grant evaluation committees including the ERC. BL has organized two scientific meetings in the reporting period.

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

BL has contributed to a patent and collaborates with the Paris-based company Cellectis. A senior group member has headed 12 clinical trials on thyroid cancer patients.

Assessment of the unit's organisation and life

The team is well organized with weekly lab meetings and seminars and fruitful interactions with other groups within the unit as evidenced by joint publications. The students and postdocs of the group expressed a high degree of satisfaction and common interest in the social well-being of the group.

Assessment of the unit's involvement in training through research

The team currently has five PhD students and four postdocs. The high quality of publications by past PhD students is evidence that the training provided to graduate students is excellent. BL has served on 15 thesis juries and 6 HDR juries.

Assessment of the strategy and the five-year plan

The proposed research is highly feasible and likely to be a scientific and organizational success, because BL has assembled a team of complementary expertise and BL has managerial experience as deputy director of the UMR217 CEA/CNRS. The scientific focus of the team will be DNA replication stress and cancerogenesis with a strong translational element. The project is highly feasible because of the outstanding qualifications, complementary experience of the team members, and state-of-the-art core facilities available at the institute.

The proposed research project is timely and ambitious, because it focuses on sources of endogenous replication stress, which are more physiologically relevant but also inherently more difficult to study compared to the high levels of replication stress often studied by treatment with exogenous genotoxic agents and replication inhibitors. The team will take a genetic approaches to study RNA/DNA hybrids by expressing RnaseH in HR-deficient cells and to study ROS by inactivation of the NADPH-oxidase.

The proposed methods are well supported by core facilities of the institute such as DNA combing, mouse labs, 2D-gel electrophoresis and microscopy. These facilities should be maintained and kept up-to-date to support the research of the team.

Senior group members with clinical experience add a strong translational aspect to the team.

Conclusion

- **Strengths and opportunities:**

Outstanding track record and equally good prospects. The research program is logical and appealing. The future directions are straightforward and promising.

- **Weaknesses and threats:**

Attention should be paid to increase international recruitment.

Insufficient technician support.

No significant international (EU, HFSP, NIH) funding.

- **Recommendations:**

Support for a full time technician for the team would make the team more efficient.

The team should be in a strong position to apply of EU funding.

Team 4 : DNA Repair

Name of team leader: Mr Murat SAPARBAEV

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, \visitors, etc.)	2	1
N6: Other contractual staff (without research duties)	2	
TOTAL N1 to N6	**6**	**3**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1*	
Theses defended	7*	
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	1	2

*theses in co-supervision with foreign universities (Universities from Kazakhstan, Russia and Poland).

• Detailed assessments

Assessment of scientific quality and outputs

This group uses E. coli, yeast and human cells to determine the molecular mechanisms that underlie DNA repair after oxidative damage. Complex DNA damages that represent a small fraction of DNA lesions, play however an important biological role as they lead to the death of the cell. The group is one of the research leaders in these processes of DNA repair and have demonstrated, among other crucial results, the role the human apurinic/apyrimidinic nuclease in nucleotide incision repair and have constructed several mutants of this enzyme that were crystallized. As DNA repair is central to cancer treatment, by chemo- as well as by radiation therapy, the work of the group fits well with the unit. The group has been extremely productive with 26 primary research publications with a constantly improving quality in the high impact factor of the journals (Mol Cell, NAR, PNAS, Oncogene). Overall, the group's track record is very good.

Assessment of the unit's academic reputation and appeal

Beside the leader, who is DR2 CNRS, there is only one permanent researcher (CR1 CNRS) in the group. The group's visibility is good and the leader received many invitations to speak at international meetings. He is editor of a Kazakhstan-based journal and has secured on a constant basis excellent collaborations with 5 national and 10 international laboratories. Several grants, not detailed (Charities, government or industry) have been secured during the period.

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

Although the group is small, there are several Television interviews mentioned, a public lecture and two journal interviews, which is good.

Assessment of the unit's organisation and life

The team looks well organized with good interactions within the team

Assessment of the unit's involvement in training through research

Excellent, for such a small group, it has/had trained 7 PhD students and several undergraduates.

Assessment of the strategy and the five-year plan

The team leader has secured or proposes to secure three grants for the next period, along which the team will develop its projects. These projects propose to extend the work that has already been conducted and are briefly described below. Two are under the responsibility of the team-leader, the third being headed by another permanent researcher of the team. It seems surprising to see such a small team already proposing to split into two sub-groups.

The projects are well described and combination of expertise of the team leader and his collaborator, and use of techniques well in hand all predict success.

Conclusion

- **Strengths and opportunities:**

The projects are clearly outlined with solid background and prospects combined with good collaborations. The team leader is well considered and this work is necessary to understand DNA repair at the molecular level, which again, however fundamental, is really important in the light of cancer radio- and chemotherapies.

- **Weaknesses and threats:**

The projects that are described as grant applications do not allow understanding the overall strategy of the group.

- **Recommendations:**

The team should remain as one team.

5 • Conduct of the visit

Visit date:

Start:	December 12, 2013 at 08h30 am
End:	December 12, 2013 at 05h45 pm

Visit site:	Institut Gustave Roussy

Conduct or programme of visit:

08h30-09h00	Closed door meeting - Presentation of AERES to the committee
09h00-09h05	Presentation of the Committee and of AERES to the lab
09h05-09h35	Presentation of the lab, achievements and projects (discussion included): Ms Patricia KANNOUCHE

Presentation of the teams (time includes questions)

09h35-10h10	Mr Filippo ROSSELLI
10h10-10h55	Mr Bernard LOPEZ
10h55-11h10	Coffe break
11h10-11h55	Ms Patricia KANNOUCHE
11h55-12h30	Mr Murat SAPARBAEV
12h30-12h45	Mr G. MAZON (emerging team, no formal evaluation)
12h45-14h00	Lunch

Discussions with the lab personnel (in parallel)

14h00-14h30	Technicians *Audience: Committee members, AERES delegate* PhD students and post-docs *Audience: Committee members, AERES delegate* Scientists *Audience: Committee members, AERES delegate, without team leaders*
14h30-14h45	Meeting with a representative of the graduate school *Audience: Committee members, AERES delegate*
14h45-15h00	Meeting with the management team *Audience: Committee members, AERES delegate*
15h00-15h30	Meeting with the representatives of the governing bodies: *Audience: Committee members, AERES delegate*
15h30-17h45	Closed-door meeting *Audience: Committee members, AERES delegate*

Specific points to be mentioned:

Mr Frédéric COIN, expert of the committee, could not attend the site visit.

6 • Supervising bodies' general comments

UNIVERSITÉ PARIS SUD

Comprendre le monde, construire l'avenir®

Le Président de l'Université Paris-Sud

à

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

Orsay, le 25 février 2014

N/Réf. : 26/14/JB/LM/AL

Objet : Rapport d'évaluation d'unité de recherche
N° S2PUR150007889

Monsieur le Directeur,

Vous m'avez transmis le 5 février dernier, le rapport d'évaluation de l'unité de recherche STABILITÉ GÉNÉTIQUE ET ONCOGÉNÈSE – n° S2PUR150007889 et je vous en remercie.

L'université prend bonne note de l'appréciation et des suggestions faites par le Comité.

Les points à améliorer seront discutés avec le directeur d'unité dans un esprit constructif pour l'avenir de la recherche à l'université.

Vous trouverez en annexe les éléments de réponse de Madame Patricia KANNOUCHE, Directrice de l'unité de recherche.

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

UNIVERSITÉ PARIS SUD

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Président

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IRCIV
LABORATOIRE STABILITE GENETIQUE ET ONCOGENESE
- UMR8200 – CNRS

Villejuif, 19th February 2014

Answer to the evaluation report established by the AERES committee:

On behalf of my colleagues, I would like to thank the committee members for the very positive evaluation and for the constructive remarks. We very much appreciated that the committee strongly supports the five-year research plan of the unit. We are also grateful for approving the merge of teams that have been proposed for the next contract.
We do think that some criticisms will help us to get better in our scientific output as well as in our international visibility. However, since this report is going to be made public we feel it necessary to correct some misunderstandings.

Management
"The Unit has no Scientific Advisory Board (SAB)".
Indeed, our unit has not its own SAB but its activities are evaluated every two years by the Gustave Roussy's International SAB.

Weaknesses and threats
"The unit has a huge deficit in ITA staff."
We completely agree with this statement. We asked our institutions every year to support our unit by providing technical staff, without success up until now. This situation becomes a real threat for the unit to meet its missions and scientific objectives.

Recommendations
- *"The committee encourages the UMR 8200 to participate in international activities."* This recommendation is quite surprising since in the report, the committee recognized the involvement of several teams in international collaborations (e.g. "The teams are very well integrated at *Institut Gustave Roussy*, and hold several collaborations at a national and international level.", "BL has engaged in several fruitful national and international collaborations"….).
- "*CR scientist from team 2 is encouraged to apply for an ERC for young investigators*". This action is currently underway.
- We note that the recruitment of a team with experience in Epigenetics would be an added value to the unit.

Team-by-team responses:

TEAM 1: "TLS Polymerases and Cancer"
We would like to thank the AERES committee members for the positive feedback and the relevant comments they gave us to improve our project. In addition to the elements highlighted in the evaluation report, we wish to clarify one misunderstanding.

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The group leader of the "Genome Plasticity and B cells" team did not replace a previous PI but rather has set up a new team in 2010. Therefore, two sentences have to be modified as follows:
- P9, 4th paragraph, line 1: Instead of *"The Genome Plasticity and B cells team experienced a change of leadership in 2010 in which a new researcher took charge replacing the previous leader",* we should read: The Genome Plasticity and B cells team is a new team formed by the group leader in 2010.
- p9, 5th paragraph, line 6: Instead of … "*since its change in leadership*"…, we should read: since its establishment, the team has focused…

TEAM 2: "FANC/BRCA Pathways and Cancers""
We wish to thank the committee members for the extremely positive assessment of the past 5-year activities of the team.
For the future, the team will loose only one of the Emeritus (and not both), who will integrate the team of the Unit director. In light of her excellent CV, the committee suggested the application of one of the CR of the team for an ERC grant. We agree and thank the committee for the suggestion and support. Obviously, if the CR will obtain an ERC starting grant, it will be impossible to maintain the same position than now in the organization chart of the team. With an ERC starting grant, to be « independent » seems mandatory. But this will not imply that we will not continue to work in a strongly coordinated and collaborative manner. Moreover, we hope to reinforce the team by the recruitment of a new CR or MCU. One of the post-docs that presently works in the team is, in our opinion, in an excellent position to obtain a permanent position.

TEAM 3: "Recombination/Repair and Cancer""
We thank the committee members for their positive evaluation of our team. We are pleased that the visiting committee has appreciated the high quality of the research that is performed by our team. Below we wish to address the weaknesses and threats perceived by the committee and comment on the suggestions made by it:

1-*"Attention should be paid to increase international recruitment."*
We suppose this should be a mistake. Indeed:
<u>In B. Lopez's group:</u>
Currently present:
- Fidel Antonio Castro-Smirnov from **Cuba**
- A-Yeong So, from **South Korea**
- Ahmed Mogherbi, from **Algeria**
- We are managing the coming of Le Thi Khanh from **Vietnam** to join the laboratory with a Vietnamese fellowship.

In the close past:
- Anastzja Grabarz from **Poland** defended her thesis in 2011
- Therese Wilhelm from **Germany** defended her thesis in 2011

We also received:
- Haijie Lu from **China** (2010-2011)
- Sylvina Hentzen from **Urugay** (2010)
- Avhijeet Kapoor from **India** (2 months in 2009)
- Nishant Shrivastava from **India** (2 months in 2009)

<u>In C. Dupuy's group:</u>
Currently present:
- Rabii Ameziane El Hassani from **Morocco**
- Ilya marinov from **Russia**

In the close past:
- Urbain Weyemi from **Benin** defended his thesis in 2010
- Myriem Boufraqech from **Morocco** defended her thesis in 2011

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- Ruy Andrade from **Brasil** (2012)
- Maria Carolina de Souza dos Santos **Brasil** (2012)

In conclusion, we received students and post-docs from different continents (Europe, Africa, Asia, US). This is probably one of the best ratio we can find in France (and in many other countries).

2- "No significant international (EU, HFSP, NIH) funding".

We thank the committee to estimate that the quality of the laboratory makes it eligible for international funding. As we have been very successful in collecting funds (even with competitive calls) for the team to work in better than decent conditions, it would be counter-productive to waste time and energy with calls for non-necessary applications. This is not an exceptional and particular situation, but represents the common situation for most of the laboratories. Consequently, we believe that this should be removed from the weaknesses or threats section, especially because this point is raised in the recommendation section (and should stay here).

3- "Insufficient technician support".

We fully agree with the committee and this is actually the main threat of the laboratory.

Specific comments from C. Dupuy's group:

Concerning "Assessment of the unit's academic reputation and appeal" and "Assessment of the unit's interaction with the social economic and cultural environment" the assessment of the "ROS and radiocarcinogenesis" team is not mentioned : organization of international congress and meetings, invited speakers in international meeting , reviewer of scientific papers, participation in training course.

TEAM 4: "DNA Repair""

We are pleased to see that our team has been positively considered by the AERES committee in terms of scientific quality and outputs, reputation and appeal, social interactions, group organization, involvement in training and long term strategy. It is remarkable that the AERES committee emphasized that, regardless of the small size of the team (only 2 tenure staff), it has demonstrated excellent achievements in terms of productivity, academic reputation and student training. However, despite all these achievements, the AERES committee does not recommend to provide any support to the team in the form of recruitment of full time technician or engineer.

Based on the fact that the size of the team is very small, the AERES committee recommends to not split it into two groups. This is apparently a misunderstanding as we didn't propose to split the team but rather to develop a new research theme: study of the role of DNA repair in epigenetic regulation. This theme has been orally presented to the committee by the CR1 researcher who has his own funds and small group of post-docs and students and this fact was not mentioned in the report.

Once again, we thank the members of the AERES Committee.

Patricia Kannouche, Ph.D.
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