# SGC - Stress génotoxiques et cancer

Rapport Hcéres

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

Section des Unités de recherche

# Evaluation report

## Research unit :

## Genotoxic stress and Cancer

## University Paris 11

March 2009

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## Research unit :

## Genotoxic stress and Cancer

## University Paris 11

| Le Président de l'AERES | Section des unités de recherche |
| --- | --- |
| | *Le Directeur* |
| Jean-François Dhainaut | Pierre Glorieux |

March 2009

# Evaluation report

## The research unit :

Name of the research unit : Stress Genotoxiques et Cancer

Requested label : UMR

N° in case of renewal : UMR 2027

Head of the research unit : M. Giuseppe BALDACCi (ex. AMOR-GUERET)

## University or school :

Université Paris 11

## Other institutions and research organization:

Institut Curie

CNRS

## Date of the visit :

December 2nd , 2008

# Members of the visiting committee

## Chairman of the commitee :

Mr Didier TROUCHE, Université Paul Sabatier,Toulouse

## Members of the visiting committee

Mrs Hannah KLEIN, New York University School of Medical, USA

Mrs Peneloppe JEGGO, Genome Damage and Stability Center, Brighton (UK)

Mr Steffen EMMERT, University of Goettingen (Germany)

Mr Peter KARRAN, University of London (UK)

Mr Etienne SCHWOB, Institut Moléculaire de Montpellier

## CNU, CoNRS, CSS INSERM, représentant INRA, INRIA, IRD.....) representatives :

Mr Jean-Pierre ROUSSET, CoNRS

# Observers

## AERES scientific representative:

Mr Philippe BOUVET, Lyon

## University or school representative:

Mr Daniel LOUVARD, Institut Curie

Mrs Anita BERSELLINI, University Paris 11

## Research organization representative (s) :

Mrs Martine DEFAIS, CNRS

# Evaluation report

## 1 • Short presentation of the research unit

- Number of lab members including researchers with teaching duties: 2
- Full time researchers: 15
- PhD students: 10, all funded
- Engineers: 7
- Technicians and administrative assistants : 4 + 2
- Number of HDR : 14
- Number of PhD students who have obtained their PhD: 8
- Average length of a PhD during the past 4 years; 4 years
- Number of PEDR : 0
- Number of "publishing" lab members: 9 out of 15

## 2 • Preparation and execution of the visit

Each committee member had received prior to the visit a report in english or in french including the description of the work performed in the last four years and the proposed projects. This report was clear and contained all the information required for an efficient preparation of the visit.

The visit began with an informal meeting with the director of the Curie institute, followed by two short public presentations by the previous laboratory director and the proposed next director. This was followed by 55 minutes scientific presentations by each team leader or proposed team leader in which they explained their main past results and their projects for the next four years. The committee was then split into three groups which had informal discussions with the students and post-doctoral scientists, with the technicians and with the permanent researchers respectively. This was followed by a closed meeting with representatives from the University, the CNRS and the Curie Institute and a closed meeting with the present and the proposed lab director. The committee then met again for final discussions and evaluation.

In summary, the visit was very informative and satisfactory, and the committee would like to thank the laboratory for this very nice organisation.

## 3 • Overall appreciation of the activity of the research unit, of its links with local, national and international partners

The research unit was previously an UMR run by the CNRS and the Curie Institute and located within the University Paris Sud Orsay. The unit would like to be also affiliated to the University Paris Sud Orsay. It was evident to the committee that the unit would greatly benefit from strengthened links to, and more support and interaction with, the university. The research unit is composed of five teams, each working in the field of the DNA damage repair and DNA damage response using yeast or cultured mammalian cells as models. Uniquely the unit has a strong focus on the damage response to oxidative stress The laboratory director, who is also a group leader will leave the laboratory. Some members of his group plan to create a new group whereas others will join one of the four existing groups in the unit. The four other groups are already existing and propose to carry on their research in the new laboratory. The committee noted that the general ambience in the laboratory is very good.

In the past four years, the laboratory has been highly dynamic with the arrival of two promising young teams, one of which is being supported by an ATIP from the CNRS. In addition, three permanent scientists have been recruited by governmental agencies. Moreover, creation of a new team led by a young researcher is proposed and recruitment of a new team is envisioned. Clearly, the laboratory is an excellent place for young researchers to become independent.

The committee praised the quality of this development as the groups or researchers who have been recently recruited are very complementary to existing groups, creating a unique highly focused scientific environment. However, the committee feels that the laboratory could benefit more from this complementarity, and collaborations within the unit should be encouraged. Special effort should be given to the recruitment of the new group, and the committee urges the laboratory to proceed rapidly to define the scientific criteria for this recruitment to ensure that the incoming group complements existing research.

During the past years, the laboratory achieved a reasonably good publication record with publications in good or very good international journals. In addition, existing international collaborations have generated publications in very good or excellent peer-reviewed journals. The committee noted the low number of publications in the top journals and encourages the laboratory and groups to promote quality rather than quantity. In addition, the committee noticed that the size of some groups may be below the critical size for effective productivity and urges the laboratory to set up a proactive search for post-doctoral fellows. As it is, the laboratory does not seem to take full advantage of the post-doctoral program of the Curie Institute and an increase in the number of post-doctoral scientists would be a significant improvement.

## 4 • Specific appreciation team by team and/or project by project

**Team 1 : Genetic Instability and carcinogenesis**

The research group characterizes Bloom's syndrome as well as the BLM gene on the clinical, functional, and molecular-genetic level. Bloom's syndrome is a very rare recessive genetic disease but important in terms of a model disease for understanding the basic mechanisms in carcinogenesis development. An open-access web-based database on Bloom's syndrome was established in 2004/2005 as well as comprehensive clinical and genetic testing. For 2010 to 2013 the group proposes to continue this type of research within established lines with multiple and rather heterogeneous approaches.

Strong points: This group has been working for many years in an interesting niche and possesses a good expertise on the BLM protein. It has successfully attracted fundings and students. Potent models have been constructed and interesting observations have been described (role of BLM in mitosis). The group has successfully developed interesting links with clinicians.

Weak points : The publication record is not very high in the past years. In addition, the group appears dangerously close to being below effective critical mass of personnel.

Recommendations : The existing research potential may gain by further focussing on certain aspects of BLM research, e.g. the combination of functional aspects with structural analyses of this RecQ helicase, and by intensifying collaborations within the research unit as well as with other researchers thereby increasing the scientific output. The group should also make strong efforts to recruit post-docs.

**Team 2 : Regulation of eucaryotic DNA replication**

The team "Regulation of eukaryotic DNA replication" will stop existing in 2009 due to the departure for new duties of its leader. Several aspects of chromosomal DNA replication are studied under physiological or stress conditions, using sophisticated genetics, biochemistry and imaging techniques in various model systems (phage T4, budding yeast, fission yeast, HeLa cells).

The strengths lie in i) the good critical mass of the team, the quality and originality of its projects; among them the identification through genetic screening using DNA Pol d mutants of secondary mutations defective in sumoylation turnover and genes (TAH18, DRE2) possibly linking chromosomal DNA replication to mitochondrial death in conditions of oxidative stress; ii) the capacity to foster several fruitful collaborations; iii) the number of publications and higher quality of some of them; iv) the strong implication of the team leader in numerous scientific committees (PhD school, CNRS, Curie Institute, …); v) the hiring of young scientists and their promotion towards independence.

The weaker points that have been noticed are a relative dispersion of projects and their frequent dependence on outside collaborations, the lack of strong leadership denoted by the few invitations to congresses or seminars, and a modest publication level (quantity + quality) for some of the group's scientists. The team would benefit from refocusing on fewer directions, striving for excellence and increasing its attractiveness for good national or foreign post-docs.

Since professional moves and restructuring units are not easy tasks, the committee would like to give credit to the Team leader and Unit Director for his smooth management and the coherent redistribution of human power to the promising younger teams.

**Team 3 : Genome stability and genotoxic stress**

Strong points :The post holder had carried out an excellent post doctoral stay in the Kolodner laboratory, which has formed the basis for the past work from 2005. This past work has been extremely focused and has resulted in two publications in good quality journals. The major focus on the peroxiredoxins represents a unique area of work that provides the post holder with an excellent "niche" for future work, since this is not a commonly pursued area of work. Although the number of publications maybe a little low, they were both of good quality, which is important. The committee considered this was a good output considering the time taken to establish a group. The committee also noted that one of the PhD students was first author on the PNAS paper and that such output is an important component of good quality PhD training.

For the future work, the proposal to continue to examine the peroxiredoxins, including the human homologues of the yeast Tsa1 protein, was a highly rated component of the future work. The analysis of the state-induced structural transitions in vivo had the potential to yield exciting results. The committee appreciated the aim to keep the work centred on studies in yeast and felt this was a wise decision for a young group. Trying to consider the differences between Prx1 and Prx11 was important and the yeast system could potentially provide valuable insight. .The proposal to examine Tah18 and Dre2 was considered to be worthwhile and had potential to be extremely good. It was difficult to evaluate because the work was still at a descriptive stage and required progressing to an exciting mechanistic understanding. Given the potential of this project it was also rated highly. Finally, the analysis of the genotoxic impact of essential oils was considered to be worthwhile and beneficial for the applicant to be engaged in a project of this nature.

In summary, the applicant was praised for a focused future application with some areas of work, particularly the work on peroxiredoxins, that had a high chance of yielding excellent publications. The applicant also appeared to be a good mentor to his students.

Weak points : The proposal to carry out a genetic screen for factors involved in translocations was considered to be an important proposal although risky and with significant difficulties. The international recognition of the group leader should be increased

Recommendations : Concerning the translocation part, the committee recommends that the post holder seeks guidance and maintains dialogue with his former mentor, Richard Kolodner. It was also suggested that a senior researcher should be involved in this project and that it was not suitable for a graduate student. It was also considered that the post holder would benefit from attending meetings and trying to have his work presented at meetings. This would also provide him with the opportunity to discuss and improve the strategy for future work of relevance to this proposal.

**Team 4 : Cell response to replication stress**

The focus of this new team will be on understanding the molecular mechanisms that protect challenged replication forks from collapsing and which permit productive fork restart and replication completion at the expense, or not, of genome integrity.

Strengths: This is clearly an important biological question with implications for our understanding of early tumorigenesis. This research area is very competitive but so far, most studies relied on interfering globally with DNA replication using drugs or conditions that affect replication fork progression at numerous sites together.

The originality and superiority of the approach taken by this team is to apply a unique, site-specific impediment to fork progression, which now allows studying the molecular events and genetic outcome of a single fork arrest. The design and previous work realized by the group leader with this system led to a very high profile paper in 2005. The approach is innovative and the combination of techniques (microscopy, chromatin-IP, analysis of replication and recombination intermediates, deep sequencing) that will be applied seems adequate to reach interesting novel conclusions. The group leader, although young, has an excellent background and knowledge of recombination and results have been obtained already along this line. A connected and original second area of research, led by a senior scientist, is the recently uncovered connection between the stress-activated protein kinase (SAPK) pathway and the homologous recombination (HR) pathway, which may be particularly relevant under conditions of oxidative stress or challenged DNA replication. Collaborations are good and funding will probably be secured.

**Weaker aspects** of the project may reside in the double fork-blocking system used, which is polar and Rtf1-dependent, thus potentially different in nature and outcome from the spontaneous or damage-induced fork stalling that may exist in precancerous cells. It might therefore be judicious to imagine other means of inducing localized fork impediments to back-up the data obtained with the first system. The sub-project aimed at identifying new players implicated in stability/restart of arrested forks seems more risky and perhaps too time-consuming (leakiness of the system, generation of deletion library). The interplay between SAPK and HR pathways is original but the experiments proposed are rather standard.

It is recommended for the new team to keep its objectives as focused as possible on the most interesting/promising leads, and to refrain of being over-ambitious in considering what can be achieved in 4 years. Care has to be taken in maintaining a group structure with clearly identified leadership to avoid the emergence of competing interests (funding, students). Since the field is moving rapidly, the committee also feels important for the junior group leader to attend at least one international conference per year and to continue fostering interactions with senior people.

**Team 5 : DNA damage, repair and mutagenic consequences – Biology of Radiations**

**Strong points :** The Biology of Radiations group possesses a strong expertise in the cellular effects of ultraviolet A (UVA) radiation. In past years, it has made significant contributions to knowledge of DNA interactions with solar and UVA radiation. In particular, the somewhat heretical, and important, notion that DNA cytclobutane pyrimidine dimers are major UVA photoproducts. The group also investigates repair of clustered DNA damages in model substrates. Both of these are important research areas. Some parts of the proposed work deal with interesting topics (the mechanism underlying S phase slow-down, Protein oxidation by UVA). Also, a major strength of the group is their internal and external collaborations. The publication record of this group remained good in the past years with one publication in PNAS and the remainder generally in good journals.

**Weak points :**

In the period under review, the group made steady, rather than spectacular progress.

The first section of the proposed work (continuation of the UVA work) is rather pedestrian. The mutagenicity of UVA is generally controversial with conflicting literature. It is not obvious how the proposed work will resolve this. Also, it was not made clear how the proposed approach will illuminate the mechanism underlying S phase slow-down. The connection between protein oxidation and replication slowdown is too speculative. No details were provided as to how the proteomic approach will work and how 'proteins of interest' will be identified.

The second section on proton therapy was poorly presented and vague. 3-D skin cultures/MutaMouse models are proposed but no indication of what will be measured. The proposed collaboration with the signalling group is good but this seems to be a straightforward radiobiology project and not particularly innovative on the Biology of Radiation group's part.

From an organisational and management view point, the group appears dangerously close to being below effective critical mass of personnel.

**Recommendations :**

The group could benefit from a prioritization of the various projects and should make strong efforts to recruit post-docs. The development of more ambitious projects should be attempted.

**Team 6 : Structure and function of RecQ helicases and their roles in genome stability and Cancer**

**Strong points :** This team has performed some interesting studies on the physical properties of RecQ-reelated DNA helicases from E. coli and mammalian cells. The team has found important and novel features of these helicases. Also to be commended is the fact that several PhD students have been part of the team and have successfully completed their PhDs. The publication record is very good, with a steady stream of publications that have students as first authors. The future plans build upon some of the findings from the past research period and should be informative. The international collaborations with groups in China are a strength.

**Weak points :** There are some areas of concern for the future direction of this group. The group as projected appears small, and may be too small to take on all of the proposed projects for the future (for example, the last project on the RIG-1 RNA helicase is of interest but seems to be stretching the team too far and will dilute the research efforts). There is also some concern as to how this team will integrate with the rest of the unit. Most of the team members appear to be from China and their ability to interact and communicate with their peer group in other teams seems limited. There is also some concern that the research is being done without a full consideration of the biology, so that it is not immediately apparent which specific human RecQ helicase will be studied in which experiment. This is important because the biological functions of the human RecQ helicases differ among each other.

**Recommendations:** The team should concentrate on its strengths, the physical and biochemical studies, but should integrate these with other teams of the unit, or with other researchers elsewhere, so that the biological impact of the proposed motifs and mutations therein can be assessed. It should be made clear from the start which RecQ helicase is being studied and why, as their in vivo roles are different. The number of projects should be limited, with priority on the first two projects, until the group has attained a size to be able to adequately take on additional projects. The publication rate is good, but an attempt to get higher profile publications, by teaming with biologists to study the in vivo impact of the findings, should be attempted. Lastly, the team leader should make a concerted effort to have all the members of his/her team interact fully with all of the other teams of the group.

# 5 • Appreciation of resources and of the life of the research unit

The funding in the laboratory is adequate and diverse, given its affiliation to both the CNRS and Curie Institute. Affiliation to the university may further increase the diversity of funding sources, with the easier recruitment of professors or assistant professors. In addition, some labs have obtained a support from the competitive ANR grants.

The laboratory belongs to the Curie Institute, which is a highly dynamic and internationally renowned environment. However, because of its location outside Paris, the unit does not seem to benefit as it should do from the Curie Institute resources. As pointed above, the ratio between post-docs and permanent researchers is low compared to the Curie Institute's standards. Moreover, attendance at the main Curie Institute's seminars in Paris is not easy given the time required to go to Paris (It takes half a day to go to a seminar), which means that the scientific communication is mainly local. Efforts to correct this by attending a seminar at least once a month in Paris would be beneficial.

The laboratory organizes internal and external seminars at a reasonable frequency, although due to the distance from Paris, the laboratory would benefit from an increase in the number of external seminars.

# 6 • Recommendations and advice

— **Strong points :**

The laboratory is composed of groups with a strong expertise in their fields;

Research in the various groups is both very focused and complementary, creating an ideal environment for top quality science;

The laboratory is very dynamic, with a lot of movements (arrival and departure of entire groups, exchange within groups);

The laboratory contains promising young researchers and promising young groups;

The general ambiance in the laboratory is very good, creating the possibility of informal discussions between members of different groups.

— **Weak points :**

- The research in some groups is too pedestrian and is not focused on the major research issues;
- The laboratory does not fully benefit from its excellent focus and complementarity;
- The projects of many groups seem too ambitious and too disperse given their size;

— **Recommendations :**

- To try to get higher profile publications;
- To encourage collaborations and contacts between the various groups, for example by setting up financial supports for collaborative projects or by favouring the co-direction of PhD students;
- To prioritize between the various projects when the size of the group is small;
- To set up special efforts to attract post-doctorate scientists. In this respect, the use of the English language in internal seminars should be encouraged;
- To increase participation of group leaders and permanent researchers at international meetings in order to improve their international recognition.

| Note de l'unité | Qualité Scientifique et production | Rayonnement et attractivité, intégration dans l'environnement | Stratégie, gouvernance et vie du laboratoire | Appréciation du projet |
|---|---|---|---|---|
| A | A | B | A | A |

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institutCurie
Ensemble, prenons le cancer de vitesse.

# UMR 2027 " Stress génotoxiques et cancer"

**Giuseppe Baldacci (directeur de l'UMR : 2006-2009)**
**Mounira Amor-Guéret (porteur du projet : 2010-2013)**

## Réponses au rapport des experts de l'AERES

## Response to point 3: « Overall appreciation of the activity of the research unit, of its links with local, national and international partners ».

*Comment about: « however, the commitee feels that the laboratory could benefit more from this complementarity, and collaborations within the unit should be encouraged ».*
We would like to stress that four articles resulting from collaborations of the different research teams have already been published. Although this could seem a low number, these papers are the starting point for an increasing number of shared papers in the future.

*Comment about: « the committee noted the low number of publications in the top journals and encouraged the laboratory and the groups to promote quality rather than quantity ».*
This observation could be explained by the recent arrival of three groups out of five. Thus, these groups need some time to accumulate enough data to publish in the top journals.

*Comment about: « as it is, the laboratory does not seem to take full advantage of the post-doctoral program of the Curie Institute ».*
We would like to stress that we obtained all the Institut Curie post-doc fellowships that we requested when we could present good non French candidates (two in the last four years). However, we also applied for other kind of funding, as it is the case for the five post-docs present in the lab.

## Responses to point 4: « Specific appreciation team by team and/or project by project ».

**Team 1: Genetic instability and carcinogenesis**
**Weak points:** *The publication record is not very high in the past years. In addition, the group appears dangerously close to being below effective critical mass of personnel.*
We would like to precise that our team was composed of four members when it joined the UMR2027 at Institut Curie in September 2004. Now, we are seven (including three permanent positions), and we expect to recruit at least one post-doc within the next months. Thus, the mass of personnel is increasing and not decreasing. Because we reached the

effective critical mass of personnel, we were able to produce several original data. Most of them have been presented in the report and during the oral presentation: part of them has already been submitted for publication, and others will be submitted soon.

**Recommendations**: *The existing research potential may gain by further focusing on certain aspects of BLM research, e.g. the combination of functional aspects with structural analyses of this RecQ helicase...*
Surprisingly, the review committee suggested to focus on a project that it is not conducted in the team (*the combination of functional aspects with structural analyses of this RecQ helicase*). Our research project is based on an original hypothesis, the "SOS-like hypothesis" that has been developed in a review (Cancer Letters, 236, 1-12, 2006). We are already testing this hypothesis through four complementary approaches, and we proposed to pursue this project during the next four years.

*... and by intensifying collaborations within the research unit as well as with other researchers thereby increasing the scientific output. The group should also make strong efforts to recruit post-docs.*
As stressed in the "Results from collaborations" section of the report, we already collaborate with the team 6 within the research unit. Our collaborative project obtained a support from the competitive INCa grant, and gave rise to three publications (Cell Cycle, 5, 1681-86, 2006; Nucleic Acids Res. 35, 6297-3610, 2007a ; Nucleic Acids Res. 35, 6029-6041, 2007b). We also collaborate with researchers out of the unit (EMBO J, 27, 1513-1524, 2008; Biochimie, 90, 1656-1666, 2008).

**Team 2: Regulation of eucaryotic DNA replication**

**The weaker points that have been noticed are:**

*A relative dispersion of projects and their frequent dependence on outside collaboration,*
This team is the largest of the research unit and comprises several staff scientists: thus, the presence of different projects should not be surprising. Outside collaborations are often due to the completion of researches started in the lab by graduate students that were later finished during a post-doc. We consider fair to allow young doctors to conclude their work in post-doc laboratories in order to increase their publication records.

*The lack of strong leadership denoted by the few invitations to congress and seminars,*
As far as the team leader is concerned, it should be noted that he was often obliged to decline invitations because of his multiple duties. In addition, if only the group leader presents the results of the group in Congresses and Seminars, it is very difficult for young scientists to make themselves known and become independent and, as noted in the report, a main aspect of our policy is to promote young scientists towards independence. In our opinion, the number of invitations to seminars and congresses of younger members of the team appear quite reasonable.

*Modest publication level (quantity+quality) for some of the group's scientists.*
It should be stressed that an additional paper was accepted only a few weeks after the the visit by the committee (Vernis L, Facca C, Delagoutte E, Soler N, Chanet R, Guiard B, Faye G, Baldacci G. A newly identified essential complex, Dre2-Tah18, controls mitochondria

effective critical mass of personnel, we were able to produce several original data. Most of them have been presented in the report and during the oral presentation: part of them has already been submitted for publication, and others will be submitted soon.

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integrity and cell death after oxidative stress in yeast. PLoS ONE. 2009;4(2):e4376. Epub 2009 Feb 5). This article has strengthened the publication records of several team members.

**Team 3: Genome stability and genotoxic stress**

**Recommendations:** *Concerning the translocation part, the committee recommends that the post holder seeks guidance and maintains dialogue with his former mentor, Richard Kolodner. It was also suggested that a senior researcher should be involved in this project and that it was not suitable for a graduate student.*

Regarding the concern on the yeast chromosomal translocation project, I would like to precise that this work will be conducted mainly by a senior researcher (Roland Chanet - Research scientist CR1 CNRS) with a strong expertise on yeast genetics.

**Team 4: Cell response to replication stress**

**Weaker aspects** "*of the project may reside in the double fork-blocking system used, which is polar and Rtf1-dependent, thus potentially different in nature and outcome from the spontaneous or damage-induced fork stalling that may exist in precancerous cells. It might therefore be judicious to imagine other means of inducing localized fork impediments to back-up the data obtained with the first system*".

I am aware that a caveat may exist in the site-specific replication arrest system that I use to investigate the molecular mechanisms that protect and promote the restart of stalled forks, since the system exploits a natural and programmed replication fork barrier. However, thank to the very well-defined outlines of the system, it remains a unique and efficient tool to dissect those mechanisms by combining different technical approaches. Knowing this caveat, conclusions drawn from the system will be backed-up using drugs that interfere with DNA replication globally. I will be also pleased to define new systems allowing getting a better mimic of "fork impediments that may exist in precancerous cells", once this will be technically addressable.

**Team 5: DNA damage, repair and mutagenic consequences – Biology of Radiations**

It appears that the committee passed over the international recognition of the work performed in the team (for instance, 7 invited conferences, among which 5 are international).

*Steady rather than spectacular progress*: we show for the first time an unconventional effect of a genotoxic agent (UVA) on cell cycle progression, i.e. the slowdown of DNA replication which does not depend on DNA damage checkpoints response (2 articles in 2008).

*Mutagenesis induced by UVA radiation in human primary keratinocytes is « pedestrian »:* Mutagenesis analysis may seem trivial. Anyhow, still in 2009, it allows to establish complex repair pathways dealing with oxidative DNA damage (Boiteux et col NAR 2009 Epub ahead of print). Mutagenesis by UVA is indeed controversial essentially due to the use of different irradiation conditions and cellular systems. The project will benefit of the exceptional savoir-faire of the team and of its collaborators. Mutagenesis by UVA in human keratinocytes is unknown and expected to differ from the previous studies involving rodent non-skin cells which do not carry melanin. As mentioned in the report, this project is funded by ANR and may have major importance in public health.

*Also, it was not made clear how the proposed approach will illuminate the mechanism underlying S phase slow-down.*
As indicated in the project, DNA combing is the best tool to survey the firing of replication origins and the progression of replication forks.

*The connection between protein oxidation and replication slowdown is too speculative.*
We have a series of data in *S. cerevisiae* that do not fit current models and could well be explained by repair and replication proteins inactivation by UVA. Combining several approaches, including yeast genetics, will allow to better estimate the role of protein oxidation in an endogenous or exogenous oxidative stress.

*No details were provided as to how the proteomic approach will work and how 'proteins of interest' will be identified.* It was indicated in the project that « total protein extracts from exposed or unexposed cells will be analyzed by bi-dimensional SDS-PAGE. The spots of interest (modified proteins) will be analyzed at the mass spectrometry proteomic platform of Institut Curie. »

Our project on protontherapy is part of a new research & development pole of radiotherapy on Orsay campus that just emerged from Institut Curie in september 2008. It is a collaborative project. Since little is known on the specific effects of protons, it is reasonable to focuse our attention on establishing the complexity of DNA damage induced by protons under conditions used in protontherapy.

*The group appears dangerously close to being below effective critical mass of personnel.* The team comprises 4-5 permanent positions. *Post-docs recruitments*: since 2001, a post-doc was regularly recruited in the team.

**Team 6: Structure and function of RecQ helicases and their role in genome stability and cancer**

**Weak points :** "*The group as projected appears small, and may be too small to take on all of the proposed projects for the future (for example, the last project on the RIG-1 RNA helicase is of interest but seems to be stretching the team too far and will dilute the research efforts). There is also some concern as to how this team will integrate with the rest of the unit. Most of the team members appear to be from China and their ability to interact and communicate with their peer group in other teams seems limited*".
We are planning to increase the recruitment of national Ph.D students and international post–docs with good communication abilities (fluent French or/and English) to strengthen our group. Certainly, we will perform our work according to our size and we will initially focus on the first two projects. The others projects will be addressed by incoming new students or post-docs. However, it is surprising to note that our fruitful collaboration with Dr. Amort-Gueret's team was ignored by the commmittee. In fact, my team and Amor-Gueret's team have together got INCA's funding three years ago and co-published three papers in international journals. We will certainly continue our collaboration.

"*There is also some concern that the research is being done without a full consideration of the biology, so that it is not immediately apparent which specific human RecQ helicase will*

*Also, it was not made clear how the proposed approach will illuminate the mechanism underlying S phase slow-down.*
As indicated in the project, DNA combing is the best tool to survey the firing of replication origins and the progression of replication forks.

*The connection between protein oxidation and replication slowdown is too speculative.*
We have a series of data in *S. cerevisiae* that do not fit current models and could well be explained by repair and replication proteins inactivation by UVA. Combining several approaches, including yeast genetics, will allow to better estimate the role of protein oxidation in an endogenous or exogenous oxidative stress.

*No details were provided as to how the proteomic approach will work and how 'proteins of interest' will be identified.* It was indicated in the project that « total protein extracts from exposed or unexposed cells will be analyzed by bi-dimensional SDS-PAGE. The spots of interest (modified proteins) will be analyzed at the mass spectrometry proteomic platform of Institut Curie. »

Our project on protontherapy is part of a new research & development pole of radiotherapy on Orsay campus that just emerged from Institut Curie in september 2008. It is a collaborative project. Since little is known on the specific effects of protons, it is reasonable to focuse our attention on establishing the complexity of DNA damage induced by protons under conditions used in protontherapy.

*The group appears dangerously close to being below effective critical mass of personnel.* The team comprises 4-5 permanent positions. *Post-docs recruitments*: since 2001, a post-doc was regularly recruited in the team.

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"*There is also some concern that the research is being done without a full consideration of the biology, so that it is not immediately apparent which specific human RecQ helicase will*

*be studied in which experiment. This is important because the biological functions of the human RecQ helicases differ among each other.*"

A fundamental question facing RecQ family helicase research is to understand how deficiency of a particular helicase gives rise to a particular syndrome since the ATPase and helicase activities are common to these helicases. We are therefore planning to characterize four different human RecQ family helicases (hRecQL, Werner, Bloom and RecQ5 proteins) with different methods to compare quantitatively DNA substrate affinity, unwind rate and processivity of these helicases towards to different substrates.

## Response to point 6: « Recommendations and advice ».

**Weak points:**

*-The research in some groups is too pedestrian an did not focused on the major research issues:*

Individual group leaders have already answered to this point.

*-The laboratory does not fully benefit from its excellent focus and complementarity:*

We underline that we have frequent meetings and many informal discussions beneficial to the work of all the teams. Also, during the last four years, for the first time we published four papers resulting from collaborations inside the unit, and others are in progress. Thus, their number will grow in the near future.

*-The projects of many groups seem too ambitious and too disperse given their size:*

In addition to individual comments by specific team's leaders, we would like to remind that some groups arrived only recently and their sizes should increase in the future.

Giuseppe Baldacci
**Directeur de l'UMR 2027 : 2006-2009**

Mounira Amor-Guéret
**Porteur du projet : 2010-2013**