Institut de radiobiologie cellulaire et moléculaire

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Institute of Cellular and Molecular Radiobiology

From the

CEA

May 2010

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et de l'enseignement supérieur

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AERES report on the research unit

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From the

CEA

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

May 2010

Research Unit

Name of the research unit: Institute of Cellular & Molecular Radiobiology

Requested label: Institut du CEA

N° in the case of renewal:

Name of the director: M. Paul-Henri ROMEO

Members of the review committee

Committee chairman

M. Bertrand NADEL, Marseille

M. P SLIJEPCEVIC, UK

Other committee members

M. JE DUMONT, Belgium

Mrs. GIPHART-GASSLER, The Netherlands

Mr. Leon MULLENDERS, The Netherlands

Mr. A OTTOLENGHI, Italy

Committee members suggested by CNU, CoNRS, CSS INSERM, CSS INRA, INRIA, IRD

Observers

AERES scientific advisor

M. Nicolas GLAICHENHAUS

University, School and Research Organization representatives

Ms. Anne FLÜRY-HERARD, CEA

Mr. Gilles BLOCH, CEA

Report

1 • Introduction

- Date and execution of the visit

The visit started on February 2nd at 1:00 pm and ended on February 3rd at 5:00 p.m. The visit started by a general presentation of the Institute by the director, followed by succinct presentations of the scientific activities from 2 of the 4 departments composing the institute (SIGRR CNRS UMR217, and SCSR, Inserm UMR967), which were evaluated in previous AERES waves (2007 and 2008). At the end of the day, the committee members met researchers, students and technicians. On February 3rd, the 5 team leaders composing the 2 remaining departments (SREIT and SRO) gave detailed presentation of 2005-2006 activities and projects for the next period (one of the labs was also evaluated in a previous AERES wave and was not presented during the visit). The visit was done in good and open manner, and all necessary information was gathered by the committee either through the presentations or face-to-face meetings.

- History and geographical localization of the research unit, and brief presentation of its field and scientific activities

The proposed Institute of Cellular and Molecular Radiobiology (iCMR) is devoted to understand the biological effects of radiations in human, and to develop preventive, monitoring and therapeutic strategies relative to the manipulation of and/or exposition to radiations. The Institute is in perfect line with the 4 missions devoted to the CEA: basic science on radiobiology, health impact of nuclear fuel, industrial requests on irradiation and contamination issues, and medical and societal requests on irradiation and contamination issues.

The iCMR regroups four departments, each being a former independent CEA or CEA-UMR/CNRS/INSERM/University unit, and reaches a critical mass of over 220 researchers, engineers and students (~70% permanent staff) working in 20 labs, most located in the Fontenay-aux-Roses CEA campus. The four departments cover a wide spectrum of research topics on radiobiology: (1) the department of Genomic Instability, Reparation and Recombination (SIGRR, led by S Boiteux) regroups 7 labs working in the field of the 3 R's, and focus on the cellular response to DNA damage upon environmental stress such as radiation exposure, using models such as bacteria, yeast, mice and human; a future direction in translational research will be driven by B Lopez; (2) the department of Stem Cells and radiations (SCSR, led by PH Roméo) regroups 7 labs focusing on the effect of genotoxic and toxic stress such as high/low doses irradiation on germinal and somatic (hematopoietic, skin, nervous) stem cells; one lab is located in Evry; (3) the department of Experimental Radiobiology and Technological Innovation (SREIT, led by S Chevillard) regroups 3 labs focusing on the short and long term effect of radiation in cancer development using human (thyroid), rodent (sarcoma, carcinoma) and pig (melanoma) tumor models, and on the radiological monitoring and protection of at risk individuals; one lab is located in Jouy-en-Josas and another one in Bruyères-le-Châtel; (4) the department of Radiobiology and Oncology (SRO, led by L Sabatier) is composed of 3 labs focusing on understanding the mechanisms of high LET radiation damage leading to genomic instability and carcinogenesis; one lab is located in Caen, and combine an open platform devoted to research using accelerated ions, and research on biological effects of radiotherapy. A number of research topics are related across departments, and some lab/department reorganization is envisioned to enhance efficacy, cooperation, and added value. The teams benefit from cutting-edge platforms devoted to radiobiology (irradiation, contamination, mouse core facility) and advanced technologies (imaging, proteomic, cytometry) most of which are implanted on the Fontenay-aux-Roses campus. The development of a bioinformatics platform dedicated to systems biology (deep sequencing) is also envisioned on the campus.

Until 2008, a large part of the global budget (up to 80%) was provided by CEA intra-mural financing of the team expenses and salaries, and by the other EPIC/EPST. In 2009, severe budgetary contraints led to a drastic reduction of the CEA subsidy and "soft" money to the labs, which will from now on mainly rely on project-based grant applications.

- Management team

The iCMR is led by the Director Paul-Henri Roméo, and is structured in four departments of 3-7 labs, each led by one of the lab heads from the department. The iCMR Director and all department heads have long-standing experience in team and unit management. Presentation and interview with the Director showed a realistic assessment of strengths and weakness of the iCMR, and of the next challenges in building up cohesion and cooperation in order to become a world-leading institute on radiobiology.

- Staff members (on the basis of the application file submitted to the AERES)

As of 30/06

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	9
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	69
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	16
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	66,2 (FTE)
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	9 (FTE)
N6: Number of Ph.D. students (Form 2.7 of the application file)	22
N7: Number of staff members with a HDR or a similar grade	24

2 • Overall appreciation on the research unit

- Summary

The Institute of Cellular and Molecular Radiobiology (iRCM) proposes to regroup on the Fontenay-aux-Roses CEA campus 4 former units already implanted on the site (to the exception of few labs), and depending on several trustees: CEA, CNRS, INSERM, INRA, University Paris-Diderot (Paris 7) and Université Paris Sud (Paris 11). Based on the available documentation and interviews of the visit, the committee feels that the strategy of federating the units as departments of a large institute fits well with the missions of the CEA and of the other agencies involved and should bring a clear added value to both the academic research and the technological innovations on radiobiology and radioprotection. With a critical mass of over 200 dedicated experts in radiobiology, combined with the unique infrastructure of the CEA relative to radiation-related facilities, technological know-how and management, the iRCM is entitled to count as a top world leader in radiobiology. This is of course providing the fact that the institute succeeds in being more than the sum of its part, which will certainly require time but also major efforts in restructuration and cooperation between labs. The committee feels that a strong focussing towards a central common theme would be an important driving incentive to achieve this goal. There was also some interrogation in the technical and/or conceptual "clusterisation" of some labs, with potential thematic overlap with other labs, sometimes within and sometimes across departments, which should either be avoided or better exploited in terms of know-how and complementarity. Other current major difficulties for the institute are (1) the dispersion of 3 of the labs in different geographic locations; (2) the confinement of the campus due to security and historical development as well as the EPIC status of the CEA preventing fluidity and turn-over of staff, in particular students and post-doc; (3) the drastic reduction of dedicated research financing from CEA. A drastic change of policy from CEA in 2009 has shortened CEA "soft" money to the labs, which will from now on mainly rely on project-based grant applications. Although some labs are already financially self-sufficient, this might change the assessment of ambitious/risky/long-term/more applied projects for others. This is to be considered in the context of the double missions devoted to the CEA: basic and applied science on radiobiology and radioprotection. In this regard, teams seem to have all latitude to

develop basic science and/or technological innovations, and the whole spectrum of balance is seen in labs from the iCMR. A large heterogeneity is consequently apparent in the scientific/applied production of the teams. A distinction between "lab" or "service/platform" falling into different type of evaluation and/or evaluation criteria might gain to be reconsidered in the future.

- Strengths and opportunities

With the regrouping of its four departments, the iCMR reaches a unique critical mass of experts on radiobiology, with excellent infrastructure and cutting-edge facilities. Furthermore, the technological "culture" and tradition of the CEA environment is a clear benefit to the generation of unique tools for high quality discoveries, and a key to their swift exploitation in industrial and clinical valorization.

- Weaknesses and threats

The confinement of the campus due to security and historical development prevents the dynamics, the opening and the turn-over required to the life of such a big Institute. Furthermore, geographical dispersion of several of the labs is a clear threat to the unity and internal dynamics of the Institute. To succeed, the iCMR must intend to be more than an "assembly of neighbors" working on a common theme. The long historical developments of the many labs composing the various departments might be a barrier to a more effective reorganization of the complementary and/or similar topics and expertise of the various members of the Institute. The future challenge of the iCMR in the next four years lies in the true common exploitation of the exceptional know-how of the staff on radio-biology, combined with the technological opportunities of the CEA environment.

- Recommendations to the head of the research unit

-Foster initiatives to create internal communication and collaboration between labs and departments in order to generate a sense of belonging to the Institute, break the "lab area", allow the exploitation of tools and know-how, complement expertise, and avoid redundancy in topics and experimental approaches;

-Encourage more involvement of researchers in teaching activities would certainly partly resolve the problem of student recruitment;

-Create a policy to encourage opening to the international arena (publications, participation to meetings, collaborations, recruitment of foreign staff, grants);

-Promote turn-over of the staff (and of scientific concepts), by opening and advertizing lab-head positions to external candidates ;

-Increase scientific visibility by promoting the production of quality (publications IF >10) over quantity.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	7/9
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	44/69
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	51/78
A4: Number of HDR granted during the past 4 years	10
A5: Number of PhD granted during the past 4 years	20

3 • Specific comments

- Appreciation on the results

The committee highly appreciates contributions that individual groups have made towards better understanding of current problems in radiation biology. These include understanding of: (a) mechanisms of radiation-induced cancers and at the gene level; (b) mechanisms of individual and cellular radiosensitivity and (c) mechanisms of genome instability and telomere dysfunction induced by radiation. Furthermore, the significant contribution was made towards development of modern radiation biology facilities. The research project of each group is generally well defined and it is clear that projects have significant impacts on their fileds. The expertise of group members covers a wide area of relevance to radiobiology including: molecular and cellular biology, molecular genetics, radiation oncology, radiation bio-physics etc.

Publication record is generally very good. However, almost all papers are published in specialist journals. Although these journals are well recognized and highly competitive in individual fields, some attempts should be made to try and publish in higher impact journals.

Some groups are highly exposed to international collaboration as exemplified by participation in several EC funded projects one of which was co-ordinated by one of the iCRM lab. This enabled development of long-term partnership with many French and European research/academic laboratories. Furthermore, industrial partnerships appear to be strong. However, it is to be noted that the association of several iCRM labs in academic consortia /industrial associations is rarely seen.

- Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners

The committee appreciates high visibility involvement of some groups in several EC funded project including: RISC RAD, GENRADT, GENRISKT, BOOSTER and DoReMi. One of these projects, namely RISC RAD, was coordinated by a iCRM lab. These projects generate significant external income which is a big boost to the iCRM budget. Furthermore, participation in numerous EC funded projects is a good indication of international competitiveness of involved groups. Some group leaders are frequently invited to speak at important conferences in the field. Some group leaders participate in conference organization.

Although the institute has expressed difficulties in student recruitment, number of PhD students have been trained during the period of assessment and many of these students pursue academic career. The international visibility of some groups through participation in various EC funded projects enables recruitment of good quality scientists.

There is strong evidence of succesful industrial partnerships which enable commercial exploitation of results and development of new projects.

- Appreciation on the strategy, management and life of the research unit

Individual groups are generally well managed as the group leaders are experienced scientists with internationally recognized expertise. However, there should be more cooperation/collaboration between individual groups within iCRM. At present there is no strong evidence of such collaboration which would certainly be beneficial for the iCRM as a whole.

The potential for generating cutting edge projects appears to be high. For example, further exploitation of gene expression signatures typical of radiation-induced tumors is a promising field of study that can potentially uncover the relevant biological mechanisms. Furthermore, use of a unique cellular system that generates chromosome breaks without telomeres could provide important insights into understanding mechanisms behind radiation induced genomic instability.

Some group leaders are involved in teaching at various institutions in France and get invitations from media when there is need to explain the impact of, for example, radiation induced cancer to the general public.

- Appreciation on the project

The projects proposed by individual groups for the next period constitute logical continuation of their previous works. The research is focused on various themes including: (a) signatures of radiation-induced tumors; (b) mechanisms of radiation induced genomic instability and interplay with cellular ageing; (c) radiation induced DNA damage response and centrosome modification; (d) the role of Ku in radiation induced DNA damage repsonse etc. Infrastructure and equipment for each project are already available within iCRM and there is no major risk associated with completion of projects.

Committee recommends stronger interaction and collaboration between individual groups as some projects show a good degree of overlap. Joining expertise and resources could result in better definition of research problems and more effective exploitation and dissemination of generated results.

Some projects are highly original and have the capacity to produce cutting edge results. The committee wants to note that examples of such projects include: (a) defining gene expression signature of radiation induced tumors and (b) exploitation of the cellular model with defined chromosome brekas lacking telomeres to understand mechanisms of radiation-induced genomic instability.

4 • Appreciation team by team

Title of the team: Cancerologie experimentale

Name of the team or project leader: Ms. Sylvie CHEVILLARD

- Staff members :

	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	6
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	2
N7: Number of staff members with a HDR or a similar grade	2

- Appreciation on the results

This team is led by a senior scientist who has a long-standing reputation in the field of molecular radiobiology. In the last four years the team has pursued following lines of research: (i) study of the early effects of radiation at the molecular and cellular levels; (ii) study of radiation-induced carcinogenesis and search for molecular signatures specific for radiation induced tumors and (iii) development of new technologies for global molecular analysis. The most significant scientific achievement of the team was identification of transcriptional signatures specific for some radiation-induced cancers. Furthermore, the team has developed: (i) a technique to quantitatively analyze post-translational protein modification and (ii) a device for protein and nucleic acid quantification without labelling.

The productivity of the team has been good with a total of 18 publications in the last four years. Publications include papers in Lung cancer (2009, 2009), BBRC (2009), International journal of cancer (2009), Carcinogenesis (2009), Journal of Radiation Research (2006, 2005). Furthermore, the team has filed 6 patent applications.

The team was able to obtain significant external funding including grants from EU, EDF and AREVA.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team has actively participated in completed EU funded projects including RISC RAD, GENRADT and GENRISKT. It is also involved in two current EU projects, MeLoDi and Booster, and it has many international collaborators. The team leader has been (i) invited to speak at 11 conferences and (ii) interviewed by TV and printed media covering the topic of radiation induced cancer. Several PhD students completed their theses during the last four years.

- Appreciation on the strategy, management and life of the team

The team appears to be well organized with evidence of good management. Some of the research topics pursued by the team are at the international cutting edge. The team leader is actively involved in teaching at several French institutions.

- Appreciation on the project

In the next period the team will focus on 4 projects:

-Characterization of mechanisms behind radiation induced carcinogenesis: This project will exploit human as well as animal models and the main focus will be to search for molecular signatures specific for radiation unduced cancers. Several active European collaborations in this area highlight the international dimension of the project. The project has a potential to be at the international cutting edge.

-Analysis of effects of radio-sensitivity at low doses: An interesting project the aim of which is to link early effects of exposure to ionizing radiation (cell survival data, apoptosis) with late effects such as genomic instability and development of cancers. A new member, who is an expert in apoptosis and DNA repair, joined the team in 2009 and will bring considerable expertise to the team.

-Development of innovative technologies: The main focus will be the LC2D project based on a chip that can segregate, identify and quantify bio-molecules in a complex fluidic mixture without labeling. The technology has been developed at CEA and the project includes collaboration with an external partner.

-Investigation of the toxicology of nano-particles: The team will focus on classifying nanoparticles based on their effects on transcriptome. The collaboration with physicists and chemists specializing in synthesis and characterization of nanoparticles has already been developed. Given the team's demonstrated expertise in transcriptome analysis the project has a potential to uncover nanoparticles related hazard to human health, if any. Therefore, this is an important project.

- Conclusion

  - Summary

A well organized and well managed team with strong international links. Some lines of research have the potential to be at the international cutting edge.

  - Strengths and opportunities

The team has successfully identified molecular signatures for several types of radiation-induced cancers. If confirmed, this could significantly impact upon current understanding of mechanisms behind radiation-induced carcinogenesis. There is also a potential for a wider societal implications given the public interest in environmental hazard due to accidental exposure to radiation. The team has shown a good activity in development of new technologies as signified by numerous patent applications. Furthermore, the team takes advantage of its scientific environment.

– Weaknesses and threats

There is a concern about dissemination of results generated by the team in the last four years, by publishing only in specialized scientific journals. There is also an impression that the team has occasionally been driven more by technology rather than scientific questions.

– Recommendations

The team certainly has a very good potential. The team members should define the key scientific questions that will be addressed in the next 4 years and use these questions to focus and prioritize their research based on hypothesis-driven approach. Given the major strength of the team in identifying molecular signatures specific for radiation-induced cancers they should use the generated information to investigate and define molecular pathways underlying radiation-induced cancers.

Title of the team: Radiobiology avec les ions accélérés

Name of the team or project leader: M. Jean-Louis LEFAIX

- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	0
N7: Number of staff members with a HDR or a similar grade	1

This team is located in Caen. The project started in 1998, the construction started in 2001 and its activity in 2004. The objective was to provide a reception facility for radiobiologists at GANIL (laboratory, irradiation equipment and staff): the use of GANIL beams, the LARIA laboratories and the on-line equipments. The facility and welcoming activities are managed by the LARIA (CEA) and CIMAP (CEA/CNRS/University) and its platform CIRIL (User facility for Interdisciplinary Research at GANIL). From 2007 the LARIA laboratory has developed research activities linked to the implementation of hadrontherapy in France (comparative studies on radiobiological response of normal or tumor human cells exposed to carbon ions versus photon irradiation.

- Appreciation on the results

LARIA is a laboratory open to the whole community. Most experiments are performed with lighter ions at energies up to ~ 95 MeV/u (C > Ca). Of note, an automated sample holder was set up in order to irradiate sequentially up to 31 culture flasks or tubes. The LARIA has three missions : (1) Support mission laboratory in radiobiology with GANIL accelerated ions (2) Hadronbiology coordination in Caen ; (3) Radiobiology resource laboratory in the ARCHADE (Advanced Resource Centre for HADrontherapy in Europe project).

The team has published 10 papers since 2005, including 4 in which the team leader is the last author: Radiation Research (2007), Semin Radiat Oncol (2007), Int J Radiat Biol (2005), J Clin Oncol (2005).

23 different scientific projects have been initiated involving 18 groups. Two projects are linked with the development of hadrontherapy (Etoile and Arcade).

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

There is a national project to implement hadrontherapy in France with a clinical center in Lyon. The pilot is INCA. LARIA is one of the few research laboratories doing research on this topic. It works closely with two research units (EA3919 and EA3214) and ENSI in Caen.

- Appreciation on the project

Two projects will be followed (1) In vivo chronic hypoxia versus normoxia oxidative stress studies, and (2) Late sequellae of radiation therapy

- Conclusion

– Summary

The team has both the role of offering facilities to the community and carry on own research activities.

The facilities that can be offered by LARIA are: to plan experiments in GANIL (information and help to make proposals; for technical realisation of the experiments (supply of the cell culture consumable); to prepare the cells before the irradiation and treat them afterwards (also providing CO2 incubators, flow boxes, Coulter cell counter); to analyse the samples after the irradiation (biochemistry, molecular biology); laboratory equipped for western blotting, immunocytochemistry, FISH, PCR); to do microscopy analysis (light and fluorescence microscopes with microphotography and image analysis); technical assistance for dosimetry and biological analysis.

The ARCHADE project can have strategic positive effect for the research community on hadrontherapy, not only in France, but in all Europe.

The synergic effect of the facilities offered also to external users and the presence of own projects, is of great importance and should remain and be enhanced, to guarantee the role of the team and of the facility within the international scientific community

– Strengths and opportunities

-Hadrotherapy is one priority for cancer treatment;

-The team provides an important and unique tool for the community for basic research on radiobiology of the radiation quality;

-The team is in a unique position to combine basic and applied research;

-The fact that the team develops its own research is important for researchers coming from the outside.

– Weaknesses and threats

The team is geographically isolated, but this is obviously due to the location of the accelerator facilities.

– Recommendations

-It should be made clear whether this lab is a platform, an applied or fundamental research laboratory or both;

-The team should rise its international profile by collaborating with other teams in France and abroad;

-Develop mechanistic approaches to improve the basic understanding of the effects that the team is studying;

-Develop collaborations with other teams in the Institute.

Team: Génétique de la radiosensibilité

Team leader: Mr. JF ANGULO-MORA

- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	1
N7: Number of staff members with a HDR or a similar grade	4

- Appreciation on the results

This team is composed of 6 permanent staff (5 CEA and 1 CNRS) and 1 PhD student. During the past 4 years, 1 postdoctoral fellow and 3 PhD students have been trained in the laboratory. The aim of the lab is to characterize genes involved in the DNA-damage response to various genomic stresses including ionizing radiation, with a special focus on understanding how cells respond to structural DNA modifications. To do so, 5 main lines of research have been developed in the past 4 years: (1) structural characterization of the human XPC and KIN17 proteins, nuclear proteins involved in cellular response to genotoxic agents. However, the role of XPC in ionizing radiation response is questionable although a role in repair of oxidative damage has been proposed. A large focus has been devoted to the structure of KIN17 and its DNA and RNA-binding functions; the main finding is its binding to replication origin in cycle-restricted phases in various cell lines; (2) study the effect of the global inhibition of miRNA biosynthesis on cell response to irradiation; given the known multiplicity of roles of miRNAs in cellular functions, the rationale of this line of research in relation to irradiation is questionable, and might be considered to stop; (3) the study of mutagenesis rates in minisatellites after irradiation in mouse germinal cells; (4) the generation of an original tool (EBV-based RNAi) allowing stable silencing of human genes, in order to silence functions such as DNA-damage sensors, or repair; this EBV-based RNAi vector technology is the most visible achievement of the lab, and has led to a patent currently commercialized by several biotech companies in Europe and the US. However, the long-term viability of this strategy has to be carefully considered in the light of recent development of lentivirus (5) the generation of a microbeam device allowing to selectively irradiate subcellular structures, and visualize repair complexes by fluorescence microscopy.

The team production since 2005 includes 4 articles as first and last authors [Mol Cell Biol (2005), Electrophoresis (2005), Mol Breed (2005), Cancer Research (2007a)], 2 articles as first author [Cancer Research (2007b) and Nucleic Acids Res (2007)], 1 article as last author [Nuclear Instruments and Methods in Physics Research (2009)] and co-signed 5 collaborative articles. Furthermore, the team is valorising one international patent.

The financing in this period has been largely dependent on in-house funding (CEA).

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team has developed some national and international collaboration with a focus on subproject 1 (XPC, KIN17). No national or international conferences were reported for the 2005-2009 period.

- ## Appreciation on the strategy, management and life of the team

This is a medium-sized team; no teaching activity is reported.

- ## Appreciation on the project

In the next 4 years, essentially all projects will be pursued (with the exception of research on the KIN17 protein and the project on stable silencing being nowadays a routine technique), although in the frame of a new driving hypothesis that upon irradiation-induced stress, centrosome-associated proteins sensing DNA damage might uncouple centrosome and chromosome cycles. The projects are now organized under 2 main research lines:

(1) Characterization of centrosome modifications after irradiation with alpha particles; The microbeam device will be exploited to detect DNA damage sensors forming foci upon irradiation, in order to monitor early changes in the centrosome of targeted and surrounding cells. The work will focus on fibroblast cell lines expressing the protein of interest fused to a fluorochrome. To assess the pathways involved in the sensing in both targeted and surrounding cells, stable fibroblast lines deficient for repair or signaling produced in the previous period will be used.

(2) Modification of centriole structure induced by changes in XPC protein expression. Modified human cell lines expressing low levels of XPC and siRNA strategies will be used to determine if a NER defect contributes to centrosomal modification via destabilization of XPC-centrin2 and/or AKAP-XPC protein complexes.

Several collaborations are anticipated for this project, but no specific policy for the allocation of resources is envisioned.

- ## Conclusion

  - ### Summary

A medium-sized team who rightly attempts to refocus on new lines of research while encountering difficulties in raising external funds and recruiting young researchers.

  - ### Strengths and opportunities

The new direction of the lab on the centriole topics is challenging, but also risky as the team enters a highly competitive field. Indeed, as proposed, it is necessary to focus the available research capacity as much as possible. The focus on XPC-centrin2 and AKAP-XPC protein complexes needs some arguments as XPC patients do not display a severe chromosomal instability phenotype.

  - ### Weaknesses and threats

-The team has not been able to compete for external funding; this threatens the opportunity to develop long-term and ambitious projects.

-The research performed in the team is very heterogeneous ;

-The team does not collaborate with other teams in the Institute despite many thematic and technological opportunities;

-The microRNA line of research should be carefully reassessed ;

  - ### Recommendations

-Investigate the role of XPC orthologs in lower eucarytotes ; notably, yeast has been a very valuable tool to dissect the genes involved in centrosome

-Set up priorities;

-Adapt tools to the scientific questions;

-Collaborate with other teams in the Institute.

Team: Radio toxicology

Team leader: Mr. Jean-Luc PONCY

- Staff members

The team is located in Bruyeres le Châtel. It includes a facilty to perform in vivo internal contaminations by inhalation in rodents. The lab includes a total of 9 members including a veterinary, an administrative staff member and technicians. The head of the lab will retire very soon.

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	7
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	0
N7: Number of staff members with a HDR or a similar grade	1

- Appreciation on the results

For the past 4 years, this team has focused on a specific goal namely to perform in vivo internal contamination by inhalation in rodents and primates with alpha emitters particularly the so called mixed uranium and plutonium oxides (MOX). During this perid this team had 5 missions (i) including a better knowledge of the specific absorption parameters for a distinct radioactive compound, (ii) better analysis of biodistribution within the body but also at tissue and cellular levels, (iii) to permit extrapolation of animal data to humans, (iv) to help the actions of physicians from the nuclear industry occupational medecine, and (v) to help the action in radioprotection. The work is subsidized by AREVA. The team has performed a series of measurements (dissolution parameters MOX, aging of compounds, decorporation after DTPA treatment) that are considered to be essential to improve risk assessment. The institute and its expertise is shared by only a few laboratories in the world i.e. labaoratoria that can do this type of inhalation work, With regard to MOX research it is in an unique position. The relevance and quality of its research is totally in line with its mission namely to support radioprotection and to serve the industrial occupational medicine. A weak point or threat for the future (as indicated by the teamleader) is that part of the facility (whole body counting tools) has to be renewed. Although the research is applied, it provides also opportunities to address very specific questions in a more mechanistic way.

During the past four years, the team has published a total of 11 papers in specialized journals including two last author papers in Radiation Research (2009) and Radiation Protection Dosimetry (2007).

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

This is a small team with a very specific scope responding to part of the missions defined by the CEA, namely radioprotection. As such, the laboratory seems somehow isolated from the international arena and classical "production" criteria. An in-depth assessment of the scope of the laboratory and its definition as a platform or a research team should be discussed before lab head replacement is acted.

The team is manily funded by AREVA.

- Appreciation on the strategy, management and life of the team

The team will continue its mission in radiotoxicology for nuclear industry. It will also develop new collaborations to assess the toxicology of nanoparticles, develop new software tools for radioprotection, study pathophysiological modifications in lungs and investigate the effect of the variation in wounds.

- Appreciation on the project

Although the team's expertise is unique in France, the project would certainly gain in developing new mechanistic approaches to improve the basic understanding of radiotoxicology of compounds used in Nuclear Industry.

- Conclusion :

– Summary

A small team that focuses on specific inhalation research aiming to improve radioprotection. The institute possesses unique expertise/facility that would be valuable for mechanistic research as well and that could provide a basis to strengthen collaborations outside the institute. Such new lines of research might facilitate to raise external funds and recruit young researchers.

– Strengths and opportunities

-This team is one of the very few places in Europe where in vivo contamination is performed and has an unique expertise/ facility in France;

-The quality of the links with a strong industrial partner that is reflected by the focused research;

-The team is in a unique position to investigate the toxicity of inhalated nanoparticles that may become a major issue.

– Weaknesses and threats

-The head of the lab will retire soon and the team is very small.

-The focused research and links with a strong industrial partner can be inhibitory toward expanding activities.

– Recommendations

-It should be made clear whether this lab is a platform, an applied or fundamental research laboratory or both;

-The team should rise its international profile by collaborating with other teams in France and abroad;

-Develop mechanistic approaches to improve the basic understanding of the effects that the team is studying;

-If basic research should be performed, the critical mass should be increased and the team should rise its international profile;

-Taking into account the opportunities for mechanistic research that could strengthen the collaboration with other research groupes, the future team leader should have a versatile interest including applied inhalation research as well as interest in basic research questions that could be addressed by the specific expertise and facilities in this institute.

Team: Laboratory of Radiation Oncology (LRO)

Team leader: Ms. Laure SABATIER

- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	3
N6: Number of Ph.D. students (Form 2.7 of the application file)	1
N7: Number of staff members with a HDR or a similar grade	1

The LRO team includes 1 researcher, 3 engineers, 3 students and 6 technicians and administrative staff.

- Appreciation on the results

The team's main expertise is in molecular and classical cytogenetics and the main focus is on biological effects of radiation including chromosomal damages, cell death and cell transformation. They have introduced and proposed to the international scientific community an original and challenging model for multistep carcinogenesis (senescence and aging) in which the loss of a telomere causes a cascade of chromosomal instability leading to chromosomal aberrations and imbalances and the unmasking of recessive mutations detected during tumour progression. The relevance of this model, which is based on data published in 2004/2005, was elaborated further and strengthened during 2005-2009. It became clear that transmission of radiation-induced damage could differ between cell types such as primary fibroblasts and keratinocytes, and age of the cells. Follow-up of the post-irradiated progeny of a single cell (keratinocyte) revealed a chromosomal instability many population doublings after irradiation and the acquisition of telomeres 25 cell divisions later. Studies were initiated to test the model in various human cancers. Using the colorectal cancer model including various grades in the multistep cancer process the team got very relevant results. A correlation was found between activation of the DNA damage response and the shortening of telomeres. Other cancer types show a more complex picture and future studies are needed to test the model in other cancers.

The team has provided a new insight into the possible mechanisms of radiation-induced carcinogenesis and has detected a biomarker as a predictor of the effect of adjuvant chemotherapy. Isolation and identification of tumour cells circulating in the blood and application of biomarkers for tumour progression are spin-offs of the fundamental work on telomerase and telomeres.

The model presented by the team is original, attractive, implicating a wave of chromosomal instability caused by a single telomere loss as a driving force in cancer and aging.

During the past 4 years, the team has published many papers in specialized peer-reviewed journals including 17 papers as last or first authors in New England Journal of Medecine (2006), The American Journal of Clinical Oncology (2009), Lung Cancer (2009), Cytogenetic and Genome Research (2008), Ann Oncol (2008), Mol Cancer Cell (2005) and Biochimie (2008). Work published in journals with high impact was the result of the strong collaboration network of the team. 14 ou of 30 papers result from a fruitful collaboration with a medical oncologist at the IGR. The team leader has also co-signed a review in Nature Cancer Review in 2009.

As also reported in the following parts, the laboratory has been coordinator or partner of several EU projects, this way establishing stable collaborations with several European laboratories.

The team has several long-term collaborations with partners in other French institutes and a long lasting collaboration with a lab of at UCSF.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team leader is a well-established scientist in the field of chromosomal instability. She frequently has been a member on scientific committees of international meetings and presented many invited talks. The team leader has been very successful in the application of funds. Apart from the salaries of CEA members in the LRO group all research is performed with external funding.

The team has hosted several French PhD students and master students.

The team has an extensive international network. It has obtained several EU fundings, including one in FP6 as a coordinator (RISC-RAD) and one in FP7 as a participant (DoReMi, as responsible of a work-package). The team is included in networks on bio-dosimetry and involved in the development of new biodosimeters. Networking and organizing RiscRad has taken most of the workload during 2005-2009. Stable collaboration with the partners has contributed largely to the scientific achievements of the last 4 years.

This is a relative small team with a strong scientific leader. The team has a motivated and dedicated technical staff suited to perform the very specialised and laborious types of experiments. The team would benefit from an additional senior scientist to intensify local scientific initiatives and collaborative projects within ICRM. An increase in the budget from IRCM (CEA) to LRO would help to develop such initiatives. The LRO unit is indispensable for ICRM and CEA.

- Appreciation on the project

The team will continue to acquire the scientific knowledge to protect humans from the adverse effects of radiation with a special focus on cancer risk. To this aim, it will study transmission of radiation-induced damages and interplay with cellular aging. The challenge is to bridge the gap between the initial radiation-induced damage and the fate of damaged cells during subsequent divisions and tumour progression.

The first project deals with the transmission of radiation-induced damages and interplay with cellular aging: Transmission of chromosomal damage will be studied in the progeny of irradiated human primary cells and related to the efficiency of DNA repair. The project aims to characterise every type of chromosomal rearrangement by multi colour FISH. It will be interesting to see, whether the results of this very laborious project will give answers on the transmission of specific initial chromosomal damage in a single cell.

The second project uses the transformed cell line with a tagged telomere, a model system that has been proven to be useful to follow the cascades of events following the loss of a single telomere. In this project the role of telomere maintenance and that of DSB repair in the genomic instability is tested. Moreover they will quantify cell survival after low dose radiation and relate the results to those of spontaneous telomere loss, and that after high dose. Quantification of tumorigenicity of the cells is included. This is an interesting project that probably will give relevant answers in the next 4 years.

A third project will involve the follow up of It two human cohorts: one in which patients were treated for haemingiomas during infancy and one of Hodgkin lymphoma patients with or without secondary cancers. By quantifying individual telomere length, the team will determine whether a correlation exists between telomere shortening and the induction of secundary radiation-induced tumours. This is a very important issue.

Project biodosimetry and confounding factors: The existence of inter-individual variation in the response to ionising radiation is well accepted. This phenomenon is of utmost importance for risk estimation, bio-dosimetry and radiotherapy. The causal relationship between short-term radiosensitivity (based on mainly chromosomal short-term assays) and that of late effects, such as secondary cancers, remains to be established. The aim of the LRO project is to contribute to the identification of a phenotype of “radiosensitivity”. It is a hard topic on which the entire scientific community has no definitive strategy.

The project on heavy metal-induced breaks is part of an ANR-funded program and less relevant for the research strategy of the team.

The development of new biodosimeters for rapid dose estimation following a large-scale radiological accident is needed and very relevant for CEA.

This project describes the role of the team in the development of multidisciplinary research activities. The team leader continues to be an active and well-recognised specialist within several European platforms, several of which will result in a direct contribution to the LRO scientific activities.

The team of LRO has been invited to be in charge of 'Infrastuctures' (WP4) within the DoReMi network of excellence and the leader will participate in the DoReMi management board. LRO aims to request the implementation of a central facility for all types of chromosome analysis in Europe. LRO could be nominated to lead such a facility.

- Conclusion :

  - Strengths and opportunities

-The team works on a very challenging subject, i.e. survival of damaged cells after the first mitosis;

-The team has a very strong expertise in cytogenetics;

-The team's approach to the role of telomere shortening is original as compared to other groups working on this issue;

-The team has developed an hypothesis-driven project on the role of telomere in genomic instability ;

-The team has been very active in coordinating research by managing and participating to European projects ;

  - Weaknesses and threats

-The team has published many papers mainly in specialized journals, and only 17 out of 30 as last or first author, probably because of the specificity of radiobiology and the several collaborations involving other European laboratories.

-A threat is the new development in breakpoint sequencing that could make cytogenetics less competitive.

  - Recommendations

-Focus on specific sets of projects with well-defined priorities ;

-Invest in the development of collaborations with other teams in the Institute.

-Given the large involvement of LRO in European scientific projects and research strategies, enhancement of the permanent staff might be of great help for their future research.

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
Non noté	Non noté	Non noté	Non noté	Non noté

Nom de l'équipe : Génétique de la radiosensibilité

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	C	Non noté	B

Nom de l'équipe : Cancérologie experimentale

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	B	A	Non noté	A

Nom de l'équipe : Laboratory of Radiation Oncology (LRO)

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	A+	Non noté	B

Nom de l'équipe :Radiobiologie avec les ions accélérés

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
Non noté	Non noté	Non noté	Non noté	Non noté

Nom de l'équipe : Radio-Toxicology

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
Non noté	Non noté	Non noté	Non noté	Non noté

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L'Administrateur Général

Monsieur Pierre GLORIEUX
Directeur de la section des Unités de recherche

AERES
20, rue Vivienne
75002 PARIS

Saclay, le 07 mai 2010

N/Réf. : DPg/AN/np/2010-136

Objet : Observations du CEA sur le rapport d'évaluation de l'« Institut de radiobiologie cellulaire et moléculaire » (IRCM)

Monsieur le Directeur,

Je remercie tout d'abord l'AERES pour la qualité du rapport d'évaluation sur l'activité de l'« Institut de radiobiologie cellulaire et moléculaire » et pour la pertinence des recommandations qui ont été faites.

En tant qu'Administrateur Général de l'Etablissement CEA, ce rapport n'appelle pas de commentaires particuliers de ma part. Je puis vous assurer que je prêterai la plus grande attention à la mise en œuvre des actions qui permettront de répondre aux recommandations formulées par l'Agence.

Veuillez agréer, Monsieur le Directeur, l'expression de mes cordiales salutations.

Bernard BIGOT

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Comments on the iRCM review

General comments

We thank the review committee for the very good report on the research unit Institute of Cellular and Molecular Radiobiology. Among the overall appreciation on the research unit and specific comments on the research unit, we found that the committee has mixed the teams that were evaluated and the Institute *per se*. Here are examples

1. ***Encourage more involvement of researchers in teaching activities***: most of the researchers of the iRCM, including members of the evaluated teams, have teaching activities. Among the iRCM's teams, very few have "problem of student recruitment". Furthermore if any problem, it is usually due to the iRCM location outside of Paris and at a lesser extent due to security constraints for the CEA centers.

2. ***The committee highly appreciates contributions ……These include understanding of: (a) mechanisms of radiation-induced cancers at the gene level; (b) mechanisms of individual and cellular radiosensitivity and (c) mechanisms of genome instability and telomere dysfunction induced by radiation.*** These topics are topics of the evaluated teams and the institute has larger topics such as stem cells and radiation or molecular mechanisms of DNA repair where the scientific production is of very high level.

3. ***Publication record is generally very good. However, almost all papers are published in specialist journals.*** Again this is true for the evaluated teams but not for the institute that published, during the five last years, 2 articles in Molecular Cell, 1 article in Nature Cell. Biology, 1 article in Nature Struct. Mol. Biology, 2 articles in Genes&Dev., 6 articles in Embo J., 1 article in J.Exp.Med., 1 article in Plos Biol. and 4 articles in PNAS.

4. ***The potential for generating cutting edge projects appears to be high. For example….***All the examples written by the committee deal with the research teams evaluated and not with the remainder of the institute.

5. ***Appreciation on the project.*** Again, the projects appreciated are only the projects of the teams evaluated and not of the other teams of the institute.

Specific comments

Team " Génétique de la radiosensibilité" (LGR)

Concerning financial aspects (Page 11 and 12): "*The financing in this period has been largely dependent on in-house funding (CEA).* "; ***"Several collaborations are anticipated for this project, but no specific policy for the allocation of resources is envisioned."***; ***"The team has not been able to compete for external funding; this threatens the opportunity to develop long term and ambitious projects."*** Our funding was essentially dependent on CEA with the exception of the salary of Dr. O. REYES, a CNRS agent. The report must mention that we have obtained external support especially from (i) EDF (Electricity of France) for radiosensitive models (10k€ in 2005 and in 2006), (ii) ARC (Association against cancer) for a micro beam device (50k€) and (iii) EDF for bystander studies (~ 45 k€ /year since 2007).

Concerning the appreciation of the results (page 11)*: "However, the role of XPC in ionizing radiation response is questionable although a role in repair of oxidative damage has been proposed."* It is known that human XPC mRNA level responds to ionizing radiation and other genotoxic stresses. What is the biological meaning of this response? We first demonstrated that XPC-deficient mice show a spontaneous increased ESTR-mutation rate. A dose of 1 Gy further increases this mutation rate, but not the exposure to ethylnitrosourea. This mutator phenotype of $XPC^{-/-}$ mice

contributes to carcinogenesis across multiple tissues during aging (Cancer Res., 2007, 67:4695-9). To test this in human cells, we silenced XPC expression in several cell lines. This significantly reduced DNA double-strand break repair (Cancer Res. 2007, 67:2526-3). These data show that XPC deficiency, in combination with other genetic defects, may contribute to impair DSB repair.

Concerning the appreciation of the project (page 12): ***"The focus on XPC-centrin2 and AKAP-XPC protein complexes needs some arguments as XPC patients do not display a severe chromosomal instability phenotype."*** XPC patients present a susceptibility to cancer 1000-fold higher than the XPC proficient population. Why cytogenetic analysis failed to detect chromosomal rearrangements in these patients? The answer is in the multistep process going from DNA lesion formation to chromosomal rearrangements. Nevertheless, it is well stated that chromosomal instability may be detected after UV-irradiation of lymphoblastic cell lines from XPC patients (Séguin et al., 1988, Am. J. Hum. Genet. 42:468-475). Several groups confirmed that XP cells of different repair capacities have different sensitivities to the chromosome breaking action of various carcinogens and mutagens (e.g. San et al., 1977, Int J Cancer., 15;20:181-7). These arguments support our proposition to determine the stability of the XPC-centrine2 (or AKAP) complexes after alpha irradiation or after the artificial modulation of the cellular concentration of XPC protein (inducible promoters).

Concerning the conclusion (page 12): ***"The team has not been able to compete for external funding; this threatens the opportunity to develop long-term and ambitious projects." "The research performed in the team is very heterogeneous***." Our projects will be performed in close collaboration with two partners: (1) The INSERM U-759 (CURIE I.) that provides us with a unique know-how on centriole detection by cryo-electro microscopy and fluorescence microscopy. The AERES evaluation of U-759 has already supported a close collaboration between our teams. (2) The Physics Sciences Division (DSM, Saclay) which supported the nuclear micro-beam irradiation project. Actually, a 3 physicists team specialized on microdosimetry handle this facility. The different and diverse competences required may give the false impression of an ambitious and heterogeneous project. The LGR laboratory will focus on the genetic and biological consequences of centrosomal modifications induced immediately after irradiation.

Team "Laboratory of Oncology" (LRO)

Page 16: ***The project on heavy metal-induced breaks is part of an ANR-funded program and less relevant for the research strategy of the team.*** Initially, our participation in the ANR project was only to fulfill the short-term needs of the project leader, with whom we collaborate with on high LET biological effects. However, after our preliminary studies have shown deleterious effects of heavy metals on telomere maintenance with telomere-tagged human cells, these interesting results have led to new avenues that are relevant to the current research strategy of our team.

Page 17:*" **the new development in breakpoint sequencing that could make cytogenetics less competitive**"*) is not in fact a threat but an advantage for us because we are able to use an integrated approach of chromosome rearrangements using classical and molecular cytogenetics for each individual cell (i.e. clonal AND non-clonal events).

Comments on the LARIA and LRT laboratories review

The LARIA laboratory is mainly a platform offering facilities to the community. We agree with the committee that the implementation of the LARIA research activity is of high interest and should remain and be enhanced. In this line, the joined effort of the three Caen's laboratories involved in hadronbiology might have the potential for generating important data in this field.

The LRT laboratory, located in Bruyères-le-Châtel, is a radiotoxicology patform. This laboratory has unique facilities and expertise to perform in vivo internal contamination by inhalation in rodents and primates with alpha emitters, particularly mixed uranium and plutonium oxides. Its mission is to serve the nuclear industry.