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

Department for the evaluation of
research units

AERES report on unit:

Molecular Radiotherapy

RAMO

Under the supervision of the following
institutions and research bodies:

Université Paris-Sud

Institut National de la Santé Et de la Recherche

Médicale - INSERM



January 2014



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

Department for the evaluation of
research units

*On behalf of AERES, pursuant to the Decree
of 3 november 2006¹,*

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

On behalf of the expert committee,

- Ms Claire RODRIGUEZ-LAFRASSE, chair of
the committee

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



Evaluation report

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

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

| | |
|--|------------------------|
| Unit name: | Molecular Radiotherapy |
| Unit acronym: | RAMO |
| Label requested: | UMR_S |
| Present no.: | UMR_S 1030 |
| Name of Director (2013-2014): | Mr Eric DEUTSCH |
| Name of Project Leader (2015-2019): | Mr Eric DEUTSCH |

Expert committee members

Chair: Ms Claire RODRIGUEZ-LAFRASSE, Université de Lyon

Experts:

- Mr Serge CANDEIAS, CEA, Grenoble
- Ms Anne LAPRIE, Institut Claudius Regaud, Toulouse (representative of CNU)
- Mr Olivier MICHEAU, INSERM UMR866, Dijon
- Mr Bernard VAN BEERS, Université Paris Diderot (representative of INSERM)
- Mr Marcel VERHEIJ, Department of Radiation Oncology, Cancer Institute, Amsterdam, The Netherlands.
- Mr Brad WOUTERS, Princess Margaret Cancer center, Toronto, Canada.

Scientific delegate representing the AERES:

Mr Daniel OLIVE

Representatives of the unit's supervising institutions and bodies:

Mr Etienne AUGÉ, Université Paris-Sud

Ms Marie-Josèphe LEROY-ZAMIA, INSERM

Mr Éric SOLARY (representative of Doctoral School of "oncologie" n°418)



1 • Introduction

History and geographical location of the unit

The Molecular Radiotherapy unit, U 1030 INSERM, situated in the Institut Gustave Roussy (IGR), was officially established in 2008. It was a follow-up to the UPRES A 21-10, created in 1998 and renewed twice (until 2007). It resulted from a partnership between IGR, Institut de Radioprotection et de Sûreté Nucléaire (IRSN) and the Université Paris-Sud. The evolution of their lines of research more oriented towards the understanding of tumor response to ionizing radiation than that of healthy tissue did not fit IRSN's objectives which decided to withdraw. At that time (2008), the Laboratory was recreated, as an INSERM unit. Both structures (UPRES A 21-10 and U 1030) were created under the leadership of Mr Jean BOURHIS. U 1030 INSERM was consolidated by the nomination of a CR1 INSERM (upgraded to DR2 since then) and of Mr Eric DEUTSCH as a PU-PH in radiotherapy. It was also affiliated to the "Institut de Recherche en Cancérologie de Villejuif" (IRCIV). In September 2012, Mr Jean BOURHIS and the DR2 left the unit and Mr Eric DEUTSCH became the director of U 1030. In March 2013, a DR2 INSERM and his team joined the unit and reinforced the cell biology/immunology axis. The unit remains attractive since two other researchers (a CR1 INSERM and a lecturer in physics) have just arrived.

U 1030 is housed in the research building at IGR and benefits from clinical/research interfaces (IGR, IRCIV) and facilities including cytometry/genomic/proteomic/metabolomic/imaging platforms and animal facilities. The arrival of the DR2 INSERM in 2013 was associated with a significant increase in their laboratory and office areas.

Management team

U 1030 is currently headed by Mr Eric DEUTSCH; an assistant is in charge of administration and budget. The laboratory council meets once every year. Lab meetings and work group meetings are organized weekly.

In the next 5 years the proposed board is Mr Eric DEUTSCH as director together with a deputy director.

AERES nomenclature

SVE1 Biologie, santé

SVE1_LS4 Physiologie, physiopathologie, biologie systémique médicale

Unit workforce

| Unit workforce | Number as at 30/06/2013 | Number as at 01/01/2015 |
|--|-------------------------|-------------------------|
| N1: Permanent professors and similar positions | 2 | 3 |
| N2: Permanent researchers from Institutions and similar positions | 2 | 3 |
| N3: Other permanent staff (without research duties) | 1 | 1 |
| N4: Other professors (Emeritus Professor, on-contract Professor, etc.) | | |
| N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.) | 5 | 5 |
| N6: Other contractual staff (without research duties) | | |
| TOTAL N1 to N6 | 10 | 12 |



| Unit workforce | Number as at 30/06/2013 | Number as at 01/01/2015 |
|--|-------------------------|-------------------------|
| Doctoral students | 11 | |
| Theses defended | 5 | |
| Postdoctoral students having spent at least 12 months in the unit* | 4 | |
| Number of Research Supervisor Qualifications (HDR) taken | | |
| Qualified research supervisors (with an HDR) or similar positions | 3 | 5 |

2 • Assessment of the unit

The general assessment of the research unit, composed of only one team, is extremely positive:

- 1) very successful over the past five years at translational research and normal tissue research;
- 2) high synergy and complementarity between the two major scientists;
- 3) high publication output, mostly in specialty journals;
- 4) significant success in attracting external funding; mostly academic and industrial funds;
- 5) international recognition and visibility of PIs in their fields, given the number of their invited lectures;
- 6) strong implication of the current and previous directors in different aspects of radiobiology and radiotherapy teaching at the national and international level;
- 7) atmosphere and the general spirit of the unit extremely positive with unanimous and enthusiastic backing for the structure and future of the unit;
- 8) strong support from Université Paris-Sud and IGR.

Based on the five year research plan and its considerable expertise in radiobiology/cell biology/radiotherapy, the unit is ideally placed to fulfill its future program of research.

Strengths and opportunities related to the context:

- the director and future co-director have recognized and complementary expertise in their respective fields and their association has resulted in the elaboration of a very ambitious and relevant project, which will benefit from the environment of the lab;
- the team has been and still is attractive for researchers, post-doctorants and students;
- the presence in the unit of 3 MDs for interface activities has been helpful in addressing clinically relevant questions;
- the good disposition of the personnel is noticeable at all levels (engineers, post-docs, Ph.D. students, technical and administrative staff);
- an intensive translational program with effective clinical transfer has been established (research unit linked to the radiation oncology and phase 1 departments), which has been attractive for pharmas to characterize and test new drug-RT combinations;
- very good funding from academic and industrial sources.



Weaknesses and threats related to the context:

- the project is addressing too many questions at the same time in the 4 different axes. The low number of full-time basic scientists may represent a limit for the development of the five-year project presented and for the supervision of PhD students;
- it is not clear who the lead scientists are for each project. It would be more efficient to have some independent leadership in the different aspects of the program, or at least define a dedicated team per axis;
- the unit has lost normal tissue radiobiology which was one of their strengths;
- although interesting, axis 4 (mainly the proton line of research) appears to be the farthest from the general focus of the unit and may jeopardize the other axes.

Recommendations

The experts committee felt that the proposed project was very well conceived and ambitious. However, it recommends setting priorities for the experiments, and defining a step-by-step working plan in the four axes. Attention must be paid to keep the project focused and on track to avoid the dispersion of manpower and increase efficiency.

Although the unit is already attractive, they should try to recruit/attract other permanent scientists to bring the program to a satisfactory conclusion, stay competitive and ensure good follow-up of PhD students (currently 5 HDR including 2 MD for 11 students).

The experts committee also recommends continuing to build on past experience with pre-clinical and clinical evaluations of new therapeutic agents. These can be incorporated in each of the axes.

It also proposes strengthening connections between the different axes of the program and prioritizing its resources on the first three axes.



3 • Detailed assessments

Assessment of scientific quality and outputs

The former unit has obtained international recognition based on excellent output and translational activities.

The publication rate was excellent during the 2008-2013 period. They published over 134 manuscripts, which is a very high score considering the size of the unit. Most publications are in specialized journals. 26 original papers in basic and preclinical science (20 as last author - 6 with an IF >5 - IFmax=7,65). 55 reviews (37 as last author including 5 reviews with IF>5 and 2 reviews with IF> 15, a Lancet IF 28 and a Nat Rev Clin Oncol IF 15). 53 clinical and translational papers, 17 as first or last author including 8 of IF 5 to 15.

Alongside the departure of some contributive team members, one should note the very good publication records of the proposed deputy director who has recently joined the team and produced 12 original papers in the reference period (4 last or 1st author including a J Exp Medicine in 2011 and 2 Cell Death Differ in 2010 and 2011) and 1 editorial in J Leukoc Biol.

The excellent scientific quality and visibility of the unit is also reflected in the numerous invitations to congresses and international conferences of the PIs.

The unit is also affiliated to and received funding from two "Initiative d'excellence" programs: the Laboratory of Excellence in Research on Medication and Therapeutic Innovation (LabEx LERMIT); the "Département Hospitalo-universitaire (DHU) Thorax Innovation"; in addition they were also funded through the Socrates program in the "Site de recherche Intégré sur le Cancer (SIRIC)" Gustave Roussy (ED Head of the DNA repair/radiation biology axis).

The past results also led to the implementation of three clinical trials and 5 patents, one of them being under licence.

They received three awards: the « Prix de l'Académie de Médecine Paul Mathieu » (2011), the « Prix de la Chancellerie des Universités » (2011) and the « Prix de l'université du Conseil Général du Val de Marne » (2012).

Assessment of the unit's academic reputation and appeal

The academic reputation of team members is excellent, including scientists and clinicians. The unit is located in one of the largest cancer institutes in Europe. This offers a unique and attractive environment for competitive molecular radiobiological research.

The former unit was especially well-known for developing novel approaches to combination therapy, and for instituting pre-clinical and clinical work to investigate novel agents. This is a major strength as attested by invitations to write manuscripts for Nature Reviews Clinical Oncology and Nature Clinical Practice in Oncology.

Normal tissue radiobiology was also a key strength of the unit. They developed a wide series of normal tissue models to study both acute and late toxicities and had become one of the leaders in this field.

The previous director was president of ESTRO and has had a major impact on radiotherapy practice and policy in Europe by stimulating pre-clinical and clinical research. Key members of the group including the current director have been very active at European meetings with many invitations to give talks and presentations and teaching in ESTRO courses.

As mentioned above, the unit participates in two "Initiative d'excellence" programs, in the SIRIC and also in 2 FP7 European projects.

Over time, the unit has been able to recruit new scientific personnel and offer a stimulating scientific environment for young researchers and clinicians.



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

It is excellent. U 1030 members fulfill an important social/societal function by participating in regular meetings with the IGR patients' committee, the "journées du patrimoine" and the "journées des donateurs". This type of activity is essential to inform patients and the general public of the progress and prospects of radiobiology/radiotherapy. They also wrote book chapters addressed to the general public (Encyclopedia Universalis). The director had two interviews published in the press (le Monde).

The unit has been able to establish partnerships with 3 start-up and one larger companies. Their interaction with industry and pharmaceutical companies is very impressive. During the period evaluated, they obtained 21 academic contracts (with 3 from EU) and 10 industrial contracts (total resources > 800 k€ for 2011 and > 1000 k€ for 2012) which permitted the development of costly research and the purchase of heavy equipment.

Five patents were submitted during the 2008-2013 period and one is under license.

Assessment of the unit's organization and life

The unit's organization, management and life are excellent. The atmosphere and the general spirit are extremely positive and enthusiastic. Lab meetings and work group meetings are organized on a weekly basis. The lab and radiation therapy/physics department meets once a week as well as a "journal club". The unit is managed through a laboratory council meeting monthly. A "house rules" document is available. Members of the unit who are MD/PhD combine lab work with clinical duties.

Mr Eric DEUTSCH is a member of the IGR's CODIR and the steering committee of the LERMIT Labex.

The discussion with the different members of the unit has led to the following points:

- PhD and Postdocs: very satisfied by mentoring support and positive general feeling. Highly motivated and dedicated;
- technicians, administrative staff and engineers: very positive about the transformation and evolution of the unit. Very good spirit and motivation;
- researchers with permanent positions: they seem to be satisfied and motivated. Two permanent researchers (1 CR1 and 1 MD) have just joined the team (2 and 3 month ago).

Assessment of the unit's involvement in training through research

There is substantial involvement in training, essentially by the previous and current directors, through Université Paris-Sud. It includes, for Mr Eric DEUTSCH, coordination and teaching of four radiation biology M2 modules and of "Diplôme de Qualification en Physique Radiologique et Médicale" (DQPRM), as well as other teaching at the national and international level (in the context of the European Network of Excellence, the European Society for Therapeutic Oncology (ESTRO) and LabEx LERMIT summer school). He also teaches in M1 at the ENS Cachan and the CEA.

A major component of teaching has also been through the direct supervision of research trainees. In the past 5 years, the lab has trained 22 Master students, 5 PhD students and 3 post-doctoral fellows. Four of the 5 PhD students have finished with papers as 1 author.

The unit is affiliated to the Doctoral School of Cancer (ED n°418 Paris-Sud) and Biology Signaling (ED n°419 Paris-Sud).

Assessment of the strategy and the five-year plan

The scientific project is meaningful, ambitious and carries great relevance both scientifically and clinically. The strategy and know-how are excellent with several outstanding components. However, the plan suffers somewhat from being too ambitious, given the current size of the lab.

Four axes have been defined: (I) cell death/senescence; (II) immunology; (III) tumor microenvironment and (IV) technology innovation. While some of its aspects (entose/entescence, cell-cell communication) are very innovative,



some are more conventional (microenvironment) but their combination and their analyses following different irradiation regimen is highly relevant and very likely to produce important results. Access to biopsies and patients' samples and close interaction with the radiotherapy/medical physics department will be instrumental in validating and translating experimental results. Synergy is expected between the cell death, immunology, and tumor microenvironment axes, with common projects and scientists.

A highly ambitious experimental plan is presented including several high throughput technologies such as "omic" methods and FlowSight Imager analyses, screening facilities and preclinical models. There could be some difficulties in implementing them and providing exploitable data in a five-year period, considering the low number of permanent scientists.

I) the first axis (cell death analysis/apoptosis-entescence) represents an example of innovative research that will be productive in the coming years but its clinical relevance needs to be demonstrated;

II) the immune axis is a very attractive line of research given the increasing evidence that radiation can trigger immunological cell death, including at abscopal sites. The systemic approach makes it valuable and it will be even more relevant if results can be related to those of the cell death axis. Furthermore, the unit is also in a very strong position to evaluate radio-immunotherapeutical regimens;

III) the goal of the third axis is to understand the impact of microenvironment factors (including H₂O₂, hypoxia and cytokines) and effectors (such as immune cells and fibroblasts) on tumor response to radiotherapy. This may represent the most complex research theme with the danger of tackling too many things at once. However, during the oral presentation they focused on HPV vaccine (2 patents) combined with irradiation, which appears to be the most novative part of this theme but not directly related to the tumor micro-environment;

IV) the technology innovation axis will focus essentially on irradiation with laser-generated ultra-intense protons or irradiation combined with nanoparticles. The proton research line appears somewhat isolated from the other axes and its relevance to the general strategy of the unit is not very clear. The risk is that it may jeopardize the other axes.

Overall, the first three axes address essential and original basic and clinical issues. We have no doubt that many additional key discoveries resulting in high impact publications will be obtained.



4 • Conduct of the visit

Visit date:

Start: Thursday 16th January 2014 at 08:30 am

End: Thursday 16th January 2014 at 05:30 pm

Visit site: Institut Gustave Roussy

Institution: INSERM U 1030

Address: 114 rue Edouard Vaillant, 94805 Villejuif cedex

Conduct or program of visit:

- 08:30 am Welcome (closed-door) experts committee with the AERES Scientific delegate (DS) (the role and procedures of AERES).
- 09:00 am Director of the unit (presentation + discussion)
- 09:30 am Presentation of the past activities and projects (2 axes) (presentation + discussion)
- Mr Jean-Luc PERFETTINI: cell death & senescence (presentation + discussion)
 - Ms Michèle MONDINI: Tumor microenvironment (presentation + discussion)
- 10:30 am Coffee Break
- 11:00 am Presentation of the past activities and projects (2 axes) (presentation + discussion)
- Mr Jean-Luc PERFETTINI: Immune response (presentation + discussion)
 - Mr Eric DEUTSCH: Technological axis & general conclusion (presentation + discussion)
- 12:00 pm Parallel meetings with personnel:
- discussions with engineers, technicians, administrative;
 - discussions with staff scientists;
 - discussions with students and post-docs.
- 12:45 pm Lunch
- 02:00 pm Discussion with the representatives of the managing bodies (INSERM, université, IGR, École Doctorale)
- 03:00 pm Private meeting of the experts committee (in presence of the DS)
- 04:00 pm Discussion with the head of the unit (if necessary)
- 04:30 pm Private meeting of the experts committee (in presence of the DS)

Specific points to be mentioned:

Ms Anne-Lise BENNACEUR, présidente du conseil scientifique de la faculté de médecine du Kremlin Bicêtre, Université Paris-Sud and Ms Claudia GALLINA, ITA (élue CSS8 INSERM) were present during the visit.



5 • Supervising bodies general comments

Le Président de l'Université Paris-Sud

à

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

Orsay, le 27 mars 2014

N/Réf. : 76/14/JB/LM/AL

Objet : Rapport d'évaluation d'unité de recherche
N° S2PUR150007962

Monsieur le Directeur,

Vous m'avez transmis le 11 mars dernier, le rapport d'évaluation de l'unité de recherche UNITE DE RADIOTHERAPIE MOLECULAIRE - n° S2PUR150007962 et je vous en remercie.

L'université se réjouit de l'appréciation portée par le Comité sur cette unité et prend bonne note de ses suggestions.

Vous trouverez en annexe les éléments de réponse de Monsieur Eric DEUTSCH, Directeur de l'unité de recherche.

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


— Jacques BITTOUN
Président
Bâtiment 300
91405 ORSAY cedex

**INSERM UNITÉ 1030
RADIOTHÉRAPIE MOLÉCULAIRE**

Pr E. Deutsch

Tél. : 33 (0) 1 42 11 65 73

Fax : 33 (0) 1 42 11 52 36

deutsch@igr.fr

Secrétaire

N. Viola

Tél. : 33 (0) 1 42 11 52 96

Fax : 33 (0) 1 42 11 52 36

viola@igr.fr

Villejuif, March 24th, 2014

Dear Members of the AERES review committee,

On behalf of our research unit, we thank the AERES committee for their site visit, for the review of our activities and for the preparation of the document that resulted. We are honoured by the extremely positive evaluation of our past accomplishments and current research efforts in the field of radiation oncology. In particular, we thank the committee for the acknowledgment of our efforts that resulted in the elaboration of a very ambitious and relevant project and the recognition of the fact that the complementary expertise of the co-directors should allow the unit to successfully realize the proposed research program that has the ambition to address the complexity of tumour responses to ionizing radiation (IR).

We acknowledge the accuracy and the pertinence of the comments made by the committee and will be more than happy to follow the recommendations and install the

best organizational frame that will boost our performances and enhance our chances to succeed.

First, in reply to the committee's request, we are happy to render more visible our managerial strategy. The proposed research axes will be developed under independent leaderships. Dr. Jean-Luc PERFETTINI will be responsible for the Cell death/Senescence axis, Pr. Eric DEUTSCH for the Immunology axis and finally a senior scientist, who will join us in the coming months, for the tumour microenvironment axis.

In reply to the recommendation “ The expert committee felt that the proposed project was very well conceived and ambitious. However, it recommends setting priorities for the experiments and defining a step-by-step working plan in the four axes”, we would like to confirm that each axis will be managed following a step-by-step working plan that will be organized and supervised by each research axis leader. The research topics that we believe to be crucial for a better understanding of the tumour (and normal tissue) responses to IR, are related to: 1/ the characterization of cell death modalities involved in the destruction of irradiated tumours, 2/ the contribution of these lethal processes to the abscopal effects of IR and 3/ the cross-talks occurring between the tumour and microenvironment cells in response to radiotherapy. Experiments related to these 3 topics will be prioritized and handled in a synergistic manner by the 3 research axes.

Our ultimate goal will be to transfer our basic scientific research to the clinic and, by having access to patient tumour biopsies, to contribute to the development of hypothesis-based translational research strategies.

In reply to the committee's comment “ The low number of full-time basic scientists may represent a limit for the development of the five-year project presented and for the supervision of PhD students”, we would like to mention that, we totally agree with the committee and we have already planned the development of an efficient leadership and manpower strategy to sustain our research activities. Months ago, we identified and started discussions with a senior scientist who should hopefully join us in order to lead the microenvironment research axis. There is no doubt, this arrival will broaden our area of expertise, bring the program to a satisfactory conclusion, help us to stay competitive and ensure the guidance of a higher number of Master degree and PhD students. Another strategy that we will implement in order to stabilize expert manpower in our laboratory, will be the stabilisation of young talented researchers through tenure track research positions at INSERM. We believe that allowing junior scientists to become permanent members of the laboratory will help the blooming of creativity and the development of our research program. Attractivity of full-time researchers will be a major objective in the long term.

The committee expressed its concern about the creation of the axis n°4 that appeared to be the farthest from the general focus of the unit and recommended the strengthening of the connections between the different axes of the program and the prioritization of the resources on the first three axes. We recognize that the technological axis n°4 is the farthest from the main stream of our research program but we have to remind the committee members the tight connection between our research unit and the radiation therapy department at Gustave Roussy. The rationale for the proposition of this axis was that we couldn't overlook technological developments

of radiation oncology since they may have a direct impact on biological processes. We believe that the development of an innovative research program at the crossroads of physics and radiobiology should lead to the definition of novel biological response read-outs applicable to the field of radiation oncology.

After careful consideration of the evaluators' comments and recommendations, we decided to continue our quest by bringing the following modifications to our proposal:

- 1/ The mainstream research program of the unit will only include the first three axes.
- 2/ The axis n°4 will be narrowed down to a research program that will be developed in collaboration with the Laboratoire d'Optique Appliquée (ENSTA/CNRS/Ecole polytechnique).
- 3/ From our laboratory side, only 2 researchers (Dr. Frédérique MEGNIN, CR1 INSERM with an expertise in hadrons and Dr. Charlotte ROBERT, MCU Paris- SUD physics) will be implicated in this collaborative program.
- 4/ The laser generated protons and Xenon parts of this technological program will be defined in a stepwise approach.
- 5/ In agreement with the evaluators, xenon and imaging parts, considered as non-priority, will not be developed during this initial phase of the program.

The committee recommended us also to continue to build on past experience with pre-clinical and clinical evaluations of new therapeutic agents. We assure the committee that we will continue to explore our preclinical expertise for the evaluation of therapeutic agents. As an illustration of this strategy, for the next five years, our plan is to amplify our collaboration with industrial groups that develop new agents

designed to be used in combinaison with IR. Various aspects of these collaborations are already included in the three research axes.

Finally, we would like to reiterate our gratitude for the confidence and support of our research efforts.

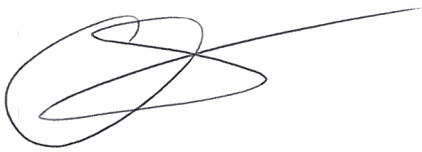
Pr Eric Deutsch

&

Dr Jean-Luc Perfettini

Director

Deputy director

A handwritten signature in black ink, consisting of a large, stylized loop followed by a horizontal line extending to the right.A handwritten signature in black ink, featuring a large, sweeping loop followed by several smaller, connected strokes.