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

Section des Unités de recherche

Evaluation report

Research unit :

Vectorology and Anticancer Therapies

University Paris 11

March 2009

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Research unit :
Vectorology and Anticancer Therapies

University Paris 11

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

March 2009

Evaluation report

The research unit :

Name of the research unit : Vectorology and Anticancer Therapies

Requested label : UMR CNRS

N° in case of renewal :

Head of the research unit : M. Lluis M. MIR

University or school :

University Paris 11

Other institutions and research organization:

CNRS

Institut Gustave Roussy

Dates of the visit :

January, 7th 2009

Members of the visiting committee

Chairman of the commitee :

Mr Philippe MOULLIER, University of Nantes

Other committee members :

Mr Bruno PITARD, University of Nantes 1

Mr Jean-Christophe PAGES, University of Tours

Mr Stephan KOCHANEK, Ulm, Germany

Mr Antoine KICHLER, University of Evry

Mr Jean-Paul BEHR, University of Strasbourg 1

Mr Marc BILLAUD, University of Lyon 1

Mrs Heidy SCHMID-ANTOMARCHI, University of Nice

Mrs Graciela PAVON-DJAVID, Institut Galilée, University of Paris 13, Villetaneuse

CNU, CoNRS, CSS INSERM, INRA, INRIA, IRD... representatives :

Mrs Marie-Agnes SARI, CNU representative

Mr Olivier JEAN-JEAN, CoNRS representative

Observers

AERES scientific representative:

Mr François-Loïc COSSET

University or school representative:

Mr Jacques BITTOUN, University representative

Mr Dominique EMILIE, University representative

Research organization representatives :

Mr Brice KERBER, CNRS representative

Mr Eric SOLARY, Institut Gustave Roussy representative

Mme Martine DEFAIS, CNRS representative

Evaluation report

1 • Short presentation of the research unit

- Total number of lab members: 42 including
  - 4 researchers from CNRS
  - 3 researchers with teaching duties: 1 PU, 1PU-PH, 1 MCU
  - 6 researchers with clinical duties from the IGR
  - 1 other researcher from BioAlliance
  - 5 postdoctoral fellows
  - 14 PhD students, all with a fellowship (Allocations du Ministère (5) ; Fondations caritatives (3) ; DGA(1) ; INCa (1) ; Cancéropôle d'Ile de France (1) ; Gouvernement syrien (1) ; Gouvernement égyptien (1) ; Gouvernement slovène et Fondation Ad Futura (1) ; Projet Européen (1).
  - 9 engineers, technicians and administrative assistants, including 5 on short term contracts
- Number of students who have obtained their PhD during the past 4 years: 7
- Number of HDR: 9
- Number of PEDR: 1
- Number of publishing researchers : 12 out of 14

2 • Preparation and execution of the visit

The organization was well prepared. The head of the unit and his team have been extremely cooperative and the entire committee has been impressed by the open minded state of each member of the team. The overall impression is that the evaluation process was smooth and efficient.

Program of the visit :

08:30 - 9:00	Arrival at the Research Pavilion, Institut Gustave-Roussy
09:00 – 9:30	Door-closed meeting
09:30 – 9:45	Door-closed meeting with the previous and the new directors
09:45 – 10:15	Presentation of the project
10:15 – 11:30	Progress report and projects of the Team
11:30 – 12:30	Lunch and posters – visit of the core facilities
12:30 – 13:00[2]	Door-closed meetings: — graduate students and post-doctoral fellows — technical staff of the laboratory (ITA, IATOS) — personnel in charge of health and security issues, GMO handling, etc..

13:00 – 13:25	Meeting with the representatives of the CNRS, University and I. Gustave-Roussy
13:25 – 13:45	Door-closed meeting with the new director
13:45 – 14:00	Coffee break
14:00 – 15:30	Door-closed meeting
15:30	Departure

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

The development of three technical platforms (viral vectors – non viral (physical) vectors – non viral (chemical) vector) and their evaluation to cancer models including the investigation of intracellular trafficking of the therapeutic materiel represent an original and attractive strategy. The overall oral presentations and the documents provided are convincing.

The team is highly competitive especially in the translational development of non viral physical vectors with current clinical applications in cancer. The PI and particularly the Director have an international recognition and are regularly invited in international conferences, e.g., Gordon Research Conf on Bioelectrochemistry (2006 and 2008), American Society for Gene Therapy, American Society for Clinical Oncology (ASCO), ECCO 2007, XVIII Int. symposium on Bioelectrochemistry and Bioenergetics, European Bioelectromagnetics Association, IEHD (Argentina), …

The publication record of the team is good to very good (69 publications, in journals with impact factors >10 for 10% and >5 for 22% of these publications), primarily of journals like J Clin. Oncol., J. Clin. Invest., Cancer Research, Molecular Therapy, Gene Therapy, Hepatology, Anticancer Research, Human Gene Therapy, Cancer Gene Therapy, J. of Steroids and Mol. Biol., Biochimica Biophysica Acta, Melanoma Research, Eur. J. of Cancer Supplements, Bioelectrochemistry, Technology in Cancer research and Treatment, PLoS One, British Journal of Pharmacology, Clin Cancer Res, Cancer Chem. Pharmacol, Cancer, Drug Metabol. Dispos., Oncogene, Br.J. Cancer, J Gene Med, J Control Release, J Neurosurgery, Neuro-Oncology.

45% of the publications are signed as first or last positions by the team members. There are heterogeneities as for the production of the PIs of the projects, which reflects different advancements in their careers. These articles are regularly cited and 5 of the PIs have H factors higher than 20.

The team was able to successfully respond to European research calls and is also a key partner to a European Network of Excellence (Clinigene). The level of funding obtained by the team is significant and several grants have been obtained from the ANR (two grants) and from the EU through small or large consortium (4 grants) on cancer/gene transfer-specific calls.

The director has been successful in gathering external investigators to support and effectively develop the three technical platforms but also their applications to cancer models. The major research highlights of the Team since 2005 are :

- Electrochemotherapy : publication of SOP's and dissemination of the treatment in Europe. Electropermeability and electrophoretic roles generated by electrical impulses during gene electrotransfer. Optimization of in vivo gene electrotransfer and irreversible electroporation for solid tumors treatment. Orphan drug status obtained for an antisense oligonucleotide designed and developed in the lab. Development of nanosecond electrical impulses for cell manipulation
- Demonstration that hexon protein from adenovirus directs the hepato-tropism and binds to coagulation factor IX and X
- Demonstration of a synergistic effect between : (i) I131-metabolic-mediated radiotherapy after gene transfer of NIS receptor, (iii) canstatine, a anti-angiogenic factor
- Identification of new genes from region 9q33-34 involved in the establishment of ependymome in children. Development of a tissue bank from pediatric tumors.

4 • Specific appreciation project by project

Cancer-targeting viral vectorology

The scientific aim is to provide recombinant adenoviruses with altered tropism after peptide insertion in the capsid structures, i.e. hexon and fiber. These peptides are chosen for their increased ability to interact with tumor cell motifs. The targeted antitumoral effect concerns inhibition of angiogenesis, conditional oncolytic adenoviruses and overexpression of the iodine transporter to combine therapy with I^{131}. The team is headed by an excellent young investigator. His program is strongly supported by the evaluation committee. However, one concern was raised, which relates to the small size of his team with respect to the many research programs that are projected. He should focus and either increase the size of his team or reduce the number of projects.

Anticancer oligonucleotides and chemotherapeutic drugs delivery using polymeric nanoparticles

The scientific aim is to develop nanoparticles as vectors for small chemical drugs and nuclei acid, i.e. siRNA for *in vitro* and *in vivo* applications. Extended pharmacological studies are proposed to understand pharmacokinetics, biodistribution and toxicity. The team demonstrates a solid work. The head of the team is a key specialist in the country and is perceived as consistent and reliable. Long and outstanding collaboration with UMR8612 « Physico-chimie, pharmacotechnie, Biopharmacie » in Chatenay-Malabry.

Exploration of new molecular targets for the papillary thyroid carcinoma

The scientific aim is to look for new molecular targets expressed in the papillary thyroid carcinoma. In particular, the presence of the abnormal fusion protein ret/PTC allows the establishment of interferant RNA (siRNA) against the specific sequence. The team has several siRNA functional candidates that need to be characterized. The head of the team is a very motivated young investigator. She was obviously well trained and seems to able to focus. However, the rationale of her project appeared questionable to the members of the committee. The team is small and yet, the competition is this particular field is tough. Other groups at IGR (« Service de Médecine Nucléaire » and also « Espèces réactives de l'oxygène et radiocarcinogénèse ») are working on the same topic, i.e. thyroid tumor models. The committee suggests that either she changes her research topic to fit in the unit overall project or she moves to a more suitable environment.

New target identification and validation in pediatric neural tumors

The scientific aim is to identify new therapeutic targets in malignant glioma and childhood ependymoma. This scientific program is done in collaboration with an European consortium « Innovative therapies for children with cancer », which is coordinated by the head of the team. The work presented is outstanding. Very professionally displayed and argumented. The committee wondered why this group wouldn't partition and set up its own research unit independant of this Unit. The obvious response is that the team is made of MD's that are also heavily involved in clinical work and therefore are looking for an appropriate scientific environment such as the one that the Director of the Unit was able to put together.

Non-viral (physical) vectors

The scientific aim is to investigate the impact of electric pulses on the cell physiology evaluating a wide variety of different pulses. This is expected to lead to an optimized approach to electro manipulate cells for gene transfer and also for direct antitumoral activity. The team provides an outstanding work. Scientifically sound and well focused. Impressive patent and licensing achievements. His work is one of the few that displays a highly successful translational development to cancer patients.

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

— Management :

The team is under reconstruction after a period of relative loose direction. The meeting with both the students and the team leaders has highlighted a need for a more consistent management for several aspects including a series of rules to share the budgets, and a policy to follow the students. According to the interviewed members of the team this has already changed.

— Human ressources :

The Director is aware that there is a need to reinforce different sub-groups by obtaining permanent positions (technicians but also researchers). Therefore, he will present a young researcher to the "CNRS concours" and he currently tries to obtain technician positions from CNRS.

— Communication :

The Director intends to restore regular scientific internal group meetings. He acknowledges that this action is necessary to favor interactions between the different sub-groups he is trying to put together.

6 • Recommendations and advice

— Strength:

- Highly motivated team.
- Consensual and well accepted leadership.
- Mostly integrated projects.
- High quality background and know-how of the subgroup leaders.
- Perfectly integrated projects within the Institut Gustave Roussy.
- Impressive experience in the comprehensive development of a therapeutic concept; i.e. from bench to bedside.
- Impressive experience in intellectual property, consolidation and industrial exploitation.

— Weakness :

Despite the lack of obvious internal conflict(s) in this large "monothématique" team, there is a lack of a comprehensive approach to prepare and anticipate the establishment of an unambiguous functional map; i.e. human resource management, financial policies, equipment policy and management, protocols and methods standardization, health and safety issues, internal meetings schedule, internal and external communication, etc… This may represent a potential threat to the cohesion of the group at a later stage.

The "Thème transversal 2" raises several questions. If the scientific question asked is sound, yet, the team is small and deserves more people to increase its competitiveness. Another comment relates to the fact that the theme requires a more appropriate scientific environment present elsewhere at Institut Gustave Roussy. In other words, due to the strong competition in this scientific field, members of the committee are inclined to think that the logic underlying the creation of this transversal project is not fully consistent, and alternatives such as a change of topic by the group leader or a move in a more suitable environment shall be considered.

— Recommendations :

In order to anticipate the establishment of the CNRS Unit, the committee recommends that the different teams gather on a regular basis with the Director to discuss and define the internal organization of the research Unit. This includes the governing rules regarding finances, grant application policy, authorship, external collaborations, lab meeting(s), participation to congresses, research project priorities, in house quality system (to what extend ?), common reagents management, etc… There is clearly a need to anticipate and organize the many issues that will be involved to sustain coherency.

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	A	B	A

IGR Institut Gustave-Roussy
De la Recherche à la Vie

UMR 8121 VECTOROLOGIE ET TRANSFERT DE GÈNES
Institut Fédératif de Recherche54

CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

Université Paris XI

Villejuif April 20th, 2009

To Pr François Loïc Cosset
Délégué Scientifique de l'AERES

Object : Reply to the report from the AERES visiting committee of the research unit **Vectorology and Anticancer Therapies**

The head of the unit and the permanent staff thank the committee for the thorough review performed and agree with the evaluation that the committee has raised on the general structure and the different projects.
I wish to comment on the following suggestions of the committee:

- Transversal theme n°2 (exploration of new molecular targets for the papillary thyroid carcinoma). As pointed out by the committee in the report, the head of this group is a very motivated young investigator. I would like to recall that she has published 34 manuscripts, and that she is the last author in 6 of them (3 of them with an IF > 5.5, and the three others with IF >3) and the first author of 14 articles. She has also 2 book chapters (1 as first author, 1 as last author).

  This investigator joined the UMR8121 in December 2007, to start a group as well as management duties at the IFSBM (directeur des etudes). Doing this, she embraced a new research subject which was **a)** fully on line with the general objectives of the UMR 8121 and of the new unit (new cancer targets and vectorization), **b)** achievable at the Institut Gustave Roussy taking into account the activity of other research groups, as pointed in the report, and the vectorization skills of the new unit. Of course, one year later, her group is still small, but very active. Since her arrival at the unit, she already got 3 grants. She is actually collaborating in the IGR with the Service de Médecine Nucléaire, with the laboratoire de Recherche Translationnelle and with CNRS FRE 2939 ("espèces réactives de l'oxygène et radiocarcinogénèse"). Together with these groups and with the UMR 8612 "Physico-chimie, pharmacotechnie, Biopharmacie" in Chatenay Malabry (already mentioned in the report), she has submitted three grant applications in 2009: to Fondation de France (13/04/09), to ANR PIRIBIO (01/04/09), with a request for a post-doc coverage, as well as to the ERC (04/05/09) with another request for a post-doc coverage. Finally, in April 2009, she has deposited a patent application on her recent results, together with UMR 8612.

  I am sure that the committee could not have all these information on her activities. Therefore I maintain my confidence in the head of this group. Nevertheless, to take into account the committee advices, I have decided to evaluate with her, on a yearly bases, the progress of her group work and her group financial situation, and appropriate actions will be undertaken if necessary.

- Communication (point 5-3), the Director agrees with the committee and has therefore initiated weekly meetings, gathering the UMR 8121 groups and the new groups that joined the UMR 8121 to form the new unit, performed since beginning of February 2009.

- Recommendations and advice (point 6-3), the Director agrees with the committee recommendations concerning the establishment of internal organization of the research unit. A chart concerning finances, grants application policy, authorship, research project priorities, human resources management is under preparation with the different group leaders.

Lluis M. Mir
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