Immunologie des tumeurs humaines : Interactions effecteurs cytokines - système tumoral

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

Human tumor immunology

University Paris 11

Mars 2009

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

mars 2009

Evaluation report

The research unit :

Name of the research unit : Human tumor immunology

Requested label : UMR_S INSERM

N° in case of renewal : U753

Head of the research unit : Mr Salem CHOUAIB

University or school :

University Paris 11

Other institutions and research organization:

INSERM

Institut Gustave Roussy (IGR)

Ecole Pratique des Hautes Etudes (EPHE)

Date of the visit :

November, 20th 2008

Members of the visiting committee

Chairman of the commitee :

Mr Joost VAN-MEERWIJK, University Toulouse 3, France

Other committee members :

Mr Cornelius MELIEF, LUMC, Leiden, The Netherlands

Mrs Angela SANTONI, University of Roma, Italy

Mr Frank TOLEDO, University Paris 6, France

Mr Marcel DECKERT, University of Nice Sophia-Antipolis, France

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

Mrs Danila VALMORI (CSS INSERM)

Mrs Marie-Christine BENÉ (CNU)

Observers

AERES scientific representative:

Mr Nicolas GLAICHENHAUS

University or school representative:

Mr Claude BOUCHAIX, University Paris 11

Mr Jacques BITTOUN, University Paris 11

Research organization representatives :

Mrs Catherine LABBÉ-JULLIE, INSERM

Mr Eric SOLARY, Institut Gustave Roussy

Evaluation report

1 • Short presentation of the research unit

- Number of lab members : 23 including
  - Number of researchers with teaching duties : 3
  - Number of full time researchers : 3
  - Number of engineers, technicians and administrative assistants : 6 (5.7 ETP)
  - Number of PhD students : 11, all funded
- Number of HDR : 5, all of them are PhD advisor
- Number of students who have obtained their PhD during the past 4 years : 8
- Number of "publishing" lab members : 6 out of 6

2 • Preparation and execution of the visit

Day 1

Time : from 16 :30 to 17 :00

Time length : 30 minutes

Door-closed meeting : Committee members, AERES representative, University and Research Organization representatives

Day 2

Time : from 8 :30 to 9h00

Time length: 30 minutes including questions

Presentation by the head of the unit : past activity and projects

Time : from 9 :00 to 10 :00

Time length: 60 minutes including questions

Presentation by the leader of team #1: past activity and projects°

Time : from 10 :00 to 11 :15

Time length: 75 minutes including questions

Presentation by the leader of team #2: past activity and projects

Coffee break from 11 :15 to 11 :30

Time : from 11 :30 to 12 :30

Time length: 60 minutes including questions

Presentation by the leader of team #3: past activity and projects

Time : from 12 :30 to 14 :00

Poster presentations and lunch

Time : from 14 :00 to 14 :30

Time length : 30 minutes

Three meetings at the same time

Meeting with PhD students and postdoctoral fellows

Meeting with engineers, technicians and administrative assistants

Meeting with researchers with permanent position

Time : from 14 :30 to 14 :45

Time length : 15 minutes

Door-closed meeting : Committee members, AERES representative, Lab director

Time : from 14 :45 to 16 :45

Time length : 120 minutes

Door-closed meeting : Committee members, AERES representative

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

This research unit works on several aspects of oncology. Team 1 focuses, with much success, its attention on cytotoxic T cell responses to tumor cells. It has identified novel tumor associated antigens and has revealed an intriguing and surprising adaptation of tumor infiltrating T cells. Team 2 investigates resistance of tumor cells to lysis by cytotoxic T cells and has made a number of fascinating observations. These two teams publish their data in good to top-level specialty journals and are very productive.

In 2010, the unit will be joined by a new team (team 3), currently EPHE/CNRS laboratory. This group works on von Hippel-Lindau (VHL) disease and renal cell carcinoma (RCC), and is interested in genetic and biological aspects. Importantly, VHL mutations are involved in RCC, and the group also works on trials of molecules acting on VHL-induced tumors. Also this group has an excellent publication record and very good reputation in its field, and it will therefore be a fine acquisition for the research unit.

The three teams will form a coherent research unit in which many intramural collaboration-possibilities are evident and described in the proposal. The proposed research plan appears pertinent and feasible. The unit has a good complementarity of experimental and clinical research and is also involved in a clinical trial. The productivity of the unit is best illustrated by its very good publication record and also includes patents. This success is made possible in part by the localization of the unit within the Gustave Roussy Institute and good support from the parent bodies (INSERM, EPHE, Paris 11 University). Its membership of the IFR54 opens the doors of several well-equipped core-facilities. The members of the unit are involved in teaching at different levels, locally, nationally, and internationally.

A note of concern relates to the rather low number of “HDR” within the unit. It also appears necessary to recruit more young scientists as well as, for team 3, technical staff.

In conclusion, this unit has developed a very interesting line of experimental and clinical research on tumor biology and has done so with much success. The evolution of the unit in the near future should ensure preservation and most probably reinforcement of its international reputation in the field of oncology.

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

Team 1 :

Research in this team mainly focuses on the assessment of immune responses to non-small cell lung carcinoma (NSCLC). The group has developed a very interesting research program in NSCLC. This has lead to the identification of novel tumor antigens that have been patented and constitute potential targets for immunotherapy. In addition the group has launched the important and original concept that tumor infiltrating lymphocytes (TIL) may adjust to the tumor environment to optimize their function, by for example downregulating inhibitory molecules such as CD5 and up-regulating the CD103 integrin. This goes against the common view that TIL are functionally deficient. The work performed in this area was viewed by the committee as of excellent quality and state of the art. It was published in several papers in good to top-level specialty journals.

The proposed research project is related to further understanding of immune responses to tumors. T cell homing to and their behavior within tumors will be studied using a xenogenic mouse model and imaging approaches. The roles of CD103 and CD5 in regulating T cell function within the tumor will be further analyzed. The team also plans to develop an anti-tumor immunotherapy for lung cancer.

The committee felt that, as most of the studies used *in vitro* cultured TIL clones, there is a need for reinforcing the experimental findings using freshly isolated polyclonal cells. In addition, the scope of the planned clinical vaccination program was viewed as limited and could be expanded to a broader set of epitopes.

Nom de l'équipe : Potentiation of cytotoxic T lymphocytes response and development of novel cancer vaccine

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	A	B	A	B

Team 2 :

This team, led by the head of the research unit, has conducted interesting and productive research concerning the elucidation of mechanisms involved in tumor resistance to cell-mediated cytotoxicity. The group established a direct link between target-susceptibility to cytotoxicity and p53 status. The group showed that cytotoxic granule exocytosis or direct incubation of target cells with granzyme B led to a stress response inducing p53 accumulation. Target cell susceptibility to CTL lysis could be inhibited by p53 siRNA. Clearly, therefore, tumor cells with altered p53 status show alterations in this pathway. Additionally, the team showed that actin cytoskeleton abnormalities in tumor cells can mediate tumor cell resistance to CTL lysis. Other resistance-mechanisms involve differential sensitivity of tumor cells to TRAIL-mediated apoptosis and loss or down-regulation of ICAM-1. The group also showed cooperation of HIF-1 and STAT-3 in hypoxic conditions to cause impairment of tumor-susceptibility to CTL-mediated cell-lysis. These and other results were published in numerous papers in good to top-level specialty journals.

The plans for future work are well structured and a direct continuation of research lines from the previous period. A relatively new and intriguing element is the study of sensitization of stromal cells, including endothelial cells, by trafficking of proteasomally digested peptides from tumor cells through gap junctions. 3D dynamic imaging will be applied to the CTL-endothelial cell interactions. This is considered to be a novel promising tool by the commission. The group proposes to conduct a detailed analysis of the role of FasL in tumor/host interactions, based on their excellent prior work. In summary, the preclinical work-plan is well-structured and innovating with proper emphasis on tumor-resistance mechanisms against CTL-mediated lysis.

The translational work of the team is very good but not particularly innovating. Moreover, there is no direct clear relationship between the preclinical and the clinical activities. The panel encourages development of translational research following from the intriguing preclinical observations.

In conclusion, the panel was impressed by the good level of research and clinical activities, but encourages better integration of these two aspects. A point of concern relates to the recruitment of young scientists, which should be improved.

Nom de l'équipe : Analysis of the molecular bases of tumor resistance to specific lysis during tumor progression

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	A	A	A	B

Team 3 :

The activity of team 3 is devoted to identification of genes involved in sporadic and hereditary renal cell carcinomas (RCC). Sporadic RCC are diagnosed when they are very advanced preventing efficient treatment. As the genes involved in hereditary RCC are also mutated in sporadic RCC, the study of both forms is relevant to better understand the molecular mechanisms responsible for kidney cancers and to design new therapeutic strategies.

This team has provided important insights in RCC, and is in an excellent position to do so in the future. A major advantage of the team is that its leader is the head of a national network on "von Hippel-Lindau (VHL) and inherited predispositions to kidney cancer", providing access to a large collection of samples from RCC patients. Also, the team leader is an internationally recognized expert in the field: he is a member of the Scientific Committee for the International VHL Symposia and has been invited to write reviews in prestigious journals such as Lancet.

The Committee appreciated the focus of this team, as well as its awareness of how to link new findings to new treatments. For example, the team is pursuing approaches to better understand the molecular mechanisms of RCC induced by VHL mutations, as well as establishing preclinical and clinical trials of molecules proposed to act on VHL-associated tumors. The fundamental and clinical aspects of the research are therefore very well integrated.

The presence of this new team in the unit is also amply justified. Indeed, the VHL protein is an ubiquitin-ligase that regulates, among others, the hypoxia-inducible factor (HIF), a factor inducing genes involved in angiogenesis and anaerobic glycolysis. A major recent finding of this team, to be published in the very prestigious NEJM, is that a regulator of HIF1a can act as a tumor suppressor preventing recurrent paragangliomas. As team 2 of this unit described the importance of HIF1a in the resistance of tumor cells to cytotoxic T lymphocytes-mediated lysis, an interaction between teams 2 and 3 may generate very interesting findings in the future.

In addition, as VHL has many other targets, its study may open the way to many new ramifications. For example VHL also regulates tumor suppressor p53, and the committee discussed that polymorphisms in the p53 pathway could be analyzed in the cohort of patients with hereditary RCC to evaluate their potential effect on tumor age of onset or agressivity.

In conclusion, the evaluation of this team is very positive. The support from the Ecole Pratique des Hautes Etudes has made it possible to recruit 3 permanent scientists, ensuring rather good core stability. With only 3 members though, the team still lacks a critical mass, and would greatly benefit from attribution of technical support.

Nom de l'équipe : Renal Carcinoma cells

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	A	A	A+	A

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

The scientific life of this unit includes several unit-wide meetings and appears quite active. The committee has not detected any problem in the acquisition of appropriate levels of funding.

6 • Recommendations and advice

— Strong points :

Strong focus on oncology.

Coherent research unit.

Good publication record.

Good complementarity of experimental and clinical research.

Several patents have been filed.

Good teaching activity.

— Weak points :

Relatively low number of HDR.

— Recommendations :

Recruit young scientists and technical staff.

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	A	B

UNIVERSITÉ
PARIS-SUD 11

Le Président de l'Université Paris-Sud 11

à

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

Orsay, le 17 avril 2009.

N/Réf. : 142/09/GCo/LM/LS

Objet : Rapport d'évaluation d'unité de recherche
N° S2100012414

Monsieur le Directeur,

Vous m'avez transmis le vingt six mars dernier, le rapport d'évaluation de l'unité de recherche « Immunologie des tumeurs humaines» - UMR S 753, 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 Salem CHOUAIB, Directeur de l'unité de recherche.

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

Guy COURRAZE
Président

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P.J. : Commentaires de M. CHOUAIB

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Ref. SC/CL/09/10

Director's comment:

We thank the AERES visiting committee for the fair assessment of our research unit. We are pleased that the committee found our unit an integrated laboratory with closely interacting teams and that our scientific production is of excellent quality.

Team1

The committee felt that, as most of the studies used in vitro cultured TIL clones, there is a need for reinforcing the experimental findings using freshly isolated polyclonal cells. In addition, the scope of the planned clinical vaccination program was viewed as limited and could be expanded to a broader set of epitopes.

- We agree with the committee that most of our studies were performed with *in vitro* cultured TIL clones and that there is a need for reinforcing our experimental findings using freshly isolated polyclonal cells. Because human lung tumor specimens are often of small sizes and are infiltrated by low numbers of tumor-infiltrating lymphocytes (TIL), such experiments cannot be performed in our previous autologous tumor model.
As an alternative, we will use lymphocytes from pleural infusions of patients suffering from lung cancers with advanced stages. We have established tumor cell lines from autologous infusions and sufficient numbers of freshly isolated polyclonal lymphocytes will be analyzed phenotypically and functionally. With regard to the scope of the planned clinical vaccination program, we are aware that using a single epitope from preprocalcitonin (ppCT) tumor antigen is limited and could be expanded to a broader set of epitopes. We will therefore identify additional epitopes from ppCT precursor protein either using the reverse immunology approach or by transfecting dendritic cells (DC) with adenoviruses bearing CALCA gene segments and stimulation of HLA-A2 PBL. The generated cytotoxic T cells will be used to identify additional epitopes using the genetic method that our group has already successfully used

Team2

The translational work of the team is very good but not particularly innovating. Moreover, there is no direct clear relationship between the preclinical and the clinical activities. The panel encourages development of translational research following from the intriguing preclinical observations.

A lot of our efforts were constantly devoted to the transfer of basic findings into clinical application thanks to a tight interaction with the clinicians of the institute. We believe that our research has resulted in two major innovations in cancer therapy:

- The unit has played for several years a facilitating and dynamic role in exploring the anti-leukemic potential of alloreactive, ex-vivo differentiated NK cells:
    - In a preclinical model using drug resistant leukemic cells transplanted in NOG mice
    - In a prospective phase I/II trial including allografted patients for myeloid leukemia

At present the kirotyping and ex-vivo expansion of allogeneic differentiated NK cells in order to overcome the difficulties related to the limited number and quality of injected NK cells are advancing and will be very shortly brought into clinical application.

- Thanks to our experience in the TNF field, our unit has played a major role in the establishment (the first in France) of a treatment protocol based on the loco-regional administration of TNF for the treatment of patients with unresectable soft tissues extremities sarcoma using isolated limb perfusion. This method features with a high response rate (> 80 %) and a similar limb salvage rate. At present, we are actively participating on the improvement of the effectiveness of locoregional administration of TNF through in vivo restoration of p53 function. Our ongoing research is focusing on the investigation of the use of mdm2 inhibitors in preclinical sarcoma models in the frame of a PHRC grant. This research axis involves several clinicians belonging to our research unit.

Salem Chouaib
Head of INSERM Unit 753