Régulation de la réponse immune, infection VIH-1 et autoimmunité

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

Regulation of the immune response, HIV-1 infection, and autoimmunity

University Paris 11

Mars 2009

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

Section des Unités de recherche

Evaluation report

Research unit :

Regulation of the immune response, HIV-1 infection, and autoimmunity

University Paris 11

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

mars 2009

Evaluation report

The research unit :

Name of the research unit : Regulation of the immune response, HIV-1 infection, and autoimmunity

Requested label : UMR_S INSERM

N° in case of renewal : U 802

Head of the research unit : Mr Marc TARDIEU

University or school :

University Paris 11

Other institutions and research organization:

INSERM

Dates of the visit :

December, 9th 2008

Members of the visiting committee

Chairman of the committee:

Mr Teunis GEIJTENBEEK, VU University, Amsterdam, The Netherlands

Other committee members:

Mrs Sarah ROWLAND-JONES, University of Oxford, UK

Mr Santos MANES, University of Madrid, Spain

Mr Mario CLERICI, University of Milano, Italy

Mr Roland LIBLAU, University Toulouse 3, France

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

Mr Bruno POZZETTO, INSERM representative

No CNU representative was available at the date of the visit

Observers

AERES scientific representative:

Mr Nicolas GLAICHENHAUS

University or school representative:

Mr Marc LOMBES, University representative

Mr Dominique EMILIE, University representative

Mr Jacques BITTOUN, University representative

Research organization representatives:

Mrs Christine TUFFEREAU, INSERM representative

Evaluation report

1 • Short presentation of the research unit

- Number of lab members including
  - Researchers with teaching duties : 7
  - Full time researchers : 4
  - Engineers, technicians, and administrative assistants : 7 including 2 part time technicians with a tenured position
  - PhD. Students : 7 including 3 MD, 1VetD, all with fellowships from INSERM, ANRS, Cancer Research Institute
- Number of HDR and of HDR who are PhD students advisors : 4
- Number of PhD students who have obtained their PhD : 8
- Average length of a PhD during the past 4 years : 44 months
- Number of "publishing" lab members : 11 out of 11

2 • Preparation and execution of the visit

- **Time :** from 10 :00 to 10 :30

  Door-closed meeting : Committee members and AERES representative
- **Time :** from 10 : 30 to 11 :00

  Presentation by Pr. Tardieu : past activity and projects
- **Time :** from 11 :00 to 12 :30

  Presentation by lab members: past activity and projects
- **Time :** from 13 :45 to 15:00

  Poster presentation
- **Time :** from 15 :00 to 15 :30

  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 15 :30 to 16 :00

  Door-closed meeting : Committee members, AERES representative, Lab director
- **Time :** from 16 :00 to 16:30

  Door-closed meeting : Committee members, AERES representative, University and Research Organization representatives
- **Time :** from 16 :30 to 18 :00

  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

The research unit has three major research lines, Pathogenesis of HIV infection, CD4 help mechanisms and Autoimmunity. Overall the different lines are productive with regard to publishing and the HIV pathogenesis and the autoimmunity project are well imbedded in national and international networks.

Among the three axes, the HIV projects are considered as good and solid, but lack some innovative angles. The cohorts available to this project are quite unique and could be explored better by focusing on innovative research questions. The CD4 help mechanisms have the advantage of studying in vivo immunology using mouse models. This has the potential of finding mechanisms that explain CD4 defects observed in HIV-1 pathogenesis. The autoimmunity research line is original and good and very productive.

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

4-1. CD4 and CD8 T cell responses in HIV patients

The work performed by this sub-team is of good quality. However, the committee members could not identify an angle that is unique to this group and/or distinguishes this group from others working in the HIV field using patient cohorts. The committee members also believe that innovative approaches are missing. The publication record of this sub-team is good. The work on identifying genes that influence HIV progression has potential but many other labs in the world are doing similar things. However, they have created a setting that will allow them to reach their goals. The work describing the association between « HIV control » and HLA-B and HLA-C alleles is interesting but many other labs are pursuing similar projects and it is very competitive. Therefore, the committee members recommend to look at more specific angles, including the mechanisms of viral immunosuppression.

4-2. Lymphopenia and CD4 help

This is an innovative and more basic and fundamental research. The move to animal models was appreciated by the committee members and might be important for all three axes. The recruitment for this team of a new researcher by INSERM this year is a sign of its vitality. The work on heterospecific help is good, solid and clearly important from a fundamental point of view. However, there is a risk that it may not be relevant to understand what happen in HIV patients. Indeed, previous research has shown that boosting CD4 T cell responses using vaccines can result in HIV reactivation. The committee members recommend investigating the role of heterospecific help in acute infection using the PRIMO cohort. Moreover, the observation that regulatory T cells may be a reservoir for HIV is interesting and should be pursued and would link this research to the HIV pathogenesis line.

4-3. Auto-immunity

The committee members appreciated the quality of the oral presentation. The group is doing cutting edge research with a strong clinical edge. The past activity was performed on a very logical basis and is very relevant from a clinical point of view. As this team has looked at autoimmune responses in patients with viral infection, the committee members think that it may be a good idea to investigate autoimmune syndromes in HIV patients with acute infection, using the PRIMO cohort.

The committee members recommend to focus on more fundamental and molecular questions including the identification of the cells that express the receptors and the identification of the cells that produce BAFF in the pathological setting. The strategy to overexpress BAFF (exon skipping) is interesting as a proof-of-principle, although its clinical utility is doubtful.

The study of genetic polymorphisms and epigenetic regulation of specific genes associated to autoimmune diseases is interesting and should be pursued..

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

The University strongly supports this research unit and is committed to encourage the development of translational research similar to the one that is performed in this research unit.

The committee members have noticed that this research unit could use more technicians and engineers, since now the necessary 'non-scientific' work is done by the PhD students. The research unit itself might try to find funding for the necessary positions, possibly with the help of INSERM or the University. The unit has been granted CR and DR researcher positions from INSERM and PU-PH and MCU-PH positions from the University.

Similarly, the research unit does not have many postdoctoral fellows and its research is primarily performed by PhD students. The committee members therefore encourage the unit to increase the number of postdoctoral fellows that are more independent in their research and might provide innovative angles based on their previous PhD research. It is especially healthy for the unit to recruit foreign postdoctoral fellows for a research period of two years. The unit is potentially very attractive for international postdoctoral fellows that are interested in both fundamental and clinical research.

6 • Recommendations and advice

— Strenghts :

- The fact that the unit is actually a single team with members working on several topics is a strength. Members of the lab who are working on different topics are helping each other. There is a lot of synergy between lab members.
- Lab members enjoy working together. The atmosphere is healthy.
- The head of the lab has a strong leadership, and has contributed to the biological material of two Science papers.
- The scientific productivity is moving upward for the unit as a whole.
- Strong links between unit members and the clinics.
- The unit has access to unique biological resources.

— Weaknesses :

- Although the publications are good, the innovative high impact publications are lacking.
- Not enough postdocs.
- Students do not have enough opportunity to attend international conferences.

— Recommendations :

- The committee believes that, for most projects, the team members need to find specific niches and ask innovative questions in order to strengthen the link between clinical and basic research.
- The committee members recommend team members to investigate the role of heterospecific help in acute HIV-1 infection using the PRIMO cohort.
- The committee members strongly recommend to recruit postdoctoral fellows, notably from foreign countries.
- Lab members must increase their visibility and try to participate in EU projects.

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 29 mai 2009.

N/Réf. 200/09/GCo/LM/LS

Objet : Rapport d'évaluation d'unité de recherche
N° S2100012390

Monsieur le Directeur,

Vous m'avez transmis le quinze avril dernier, le rapport d'évaluation de l'unité de recherche « Régulation de la réponse immune, infection VIH-1 et auto-immunité » - UMR S 802, 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.

Les points à améliorer seront discutés avec le directeur d'unité dans un esprit constructif pour l'avenir de la recherche à l'université.

Vous trouverez en annexe les éléments de réponse de monsieur Marc TARDIEU, Directeur de l'unité de recherche.

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

Guy COURRAZE
Président

UNIVERSITÉ PARIS-SUD 11 - Présidence - 91405 ORSAY CEDEX

P.J. : Commentaires de M. M. TARDIEU

Pr. Guy COUARRAZE - Université Paris-Sud 11 Bât. 300 - 91405-Orsay-cedex
Tél : 01 69 15 74 06 – Fax : 01 69 15 61 03 - e-mail : president@u-psud.fr
Siège : Université Paris-Sud 11 - 91405 Orsay cedex - http://www.u-psud.fr

Instituts thématiques

Inserm

Institut national
de la santé et de la recherche médicale

Equipe de Recherche U 802
Immunité antivirale systémique et cérébrale

Mme Laure MARTINEAU
Responsable du Service Centrale
de la Recherche
Université PARIS SUD
Bât 300
91405 ORSAY

Bicêtre, le 21 avril 2009

Objet : Commentaires et réponses au rapport d'évaluation de l'AERES
(EVAL 0911101C-S2100012990-UR-PPRELIM)

Madame,

Nous avons lu avec grande attention le rapport du comité de visite de l'AERES. Nous sommes d'accord avec les données quantitatives exprimées et étudions avec attention les recommandations faites.
Nous avons noté que l'AERES nous avait suivis dans notre désir de constituer une équipe monothématique et dans notre choix de sujets nouveaux (concernant l'aide CD4 et l'autoimmunité) dont la qualité a été soulignée. L'AERES a aussi noté la progression de nos publications et la force de notre situation d'interface avec l'activité clinique.

Nous désirons commenter sur les points de faiblesse :

- L'originalité de notre travail sur l'infection VIH-1 est apparue insuffisante. Nous avons été les premiers à décrire les patients « HIV controllers » conjointement avec une équipe américaine, à identifier le rôle clé des lymphocytes T8 de ces patients (publication PNAS) et ce sujet est devenu un enjeu majeur dans l'étude de la physiopathologie de l'infection VIH-1. Ce sujet est certes l'un des plus compétitifs dans le domaine mais notre travail est tout à fait dans la compétition. L'abord génétique nous parait original de même que l'étude fondamentale des mécanismes de l'aide CD4 et de la lymphopénie appliquée à l'infection VIH-1.
- Le manque de publications de « high impact ». Il faut malgré tout noter dans notre liste de publications 3 publications dans PNAS et 1 récente dans le J. Clin. Invest. (1er et/ou dernier auteurs) et des participations importantes à 2 articles dans Science, 1 dans Nature médicine et 1 dans N Engl J Med. Les rapporteurs notent par ailleurs la qualité globale de nos publications (19 nouvelles publications ont été publiées depuis la mise en ligne du dossier).

Université Paris XI

Equipe de Recherche U 802
Faculté de Médecine Paris Sud
63 rue Gabriel Péri
94276 Le Kremlin Bicêtre Cedex

Tel : 01.49.59.67.55 ou 67 20

Fax : 01.49.59.67.53 ou 67 24

Instituts thématiques
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Equipe de Recherche U 802
Immunité antivirale systémique et cérébrale

- Post-doc et étudiants : s'il est exact que lors de la visite il n'y avait pas de post-doc en cours au laboratoire, il y en a eu dans le passé dont le meilleur exemple est Ch. Bourgeois ensuite recrutée à l'INSERM. Deux autres post-docs arrivent ces jours-ci. Tous les étudiants du laboratoire ont toujours présenté leur travaux dans des congrès internationaux (ce n'est pas le cas des ingénieurs et techniciens, ce qui est probablement la source de l'erreur du comité d'évaluation).

Nous sommes globalement encouragés dans notre travail par les commentaires du comité d'évaluation de l'AERES et nous le remercions de son travail et de la qualité de la journée d'évaluation.

Soyez assurée Madame, de toute notre considération.

Marc TARDIEU
Directeur UMR S802

Université Paris XI

Equipe de Recherche U 802
Faculté de Médecine Paris Sud
63 rue Gabriel Péri
94276 Le Kremlin Bicêtre Cedex

Tel : 01.49.59.67.55 ou 67 20

Fax : 01.49.59.67.53 ou 67 24