Développement du système immunitaire

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

U783 Développement du système immunitaire

University Paris 5

February 2009

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et de l'enseignement supérieur

Section des Unités de recherche

Evaluation report

Research unit :

U783 Développement du système immunitaire

University Paris 5

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 : Développement du système immunitaire

Requested label : UMR_S INSERM

N° in case of renewal : U783

Head of the research unit : Mrs Claude-Agnès REYNAUD

University or school :

University Paris 5

Other institutions and research organization:

INSERM

Date of the visit :

February, 3rd 2009

Members of the visiting committee

Chairman of the commitee :

Mr Michael NEUBERGER, MRC-LMB, Cambridge, UK

Other committee members :

Mr Andreas RADBRUCH, Berlin, Germany

Mr Bertrand NADEL, University Aix-Marseille 2, France

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

Mrs Claudine SCHIFF, CSS INSERM representative

Mr Pierre GALANAUD, CNU representative

Observers

AERES scientific representative:

Mr Marc BONNEVILLE

University or school representative:

Mr Bruno VARET, University Paris 5

Research organization representative :

Mrs Christine TUFFEREAU, INSERM

Evaluation report

1 • Short presentation of the research unit

- Number of lab members : 17, including
  - 2 researchers with teaching duties
  - 4 full time researchers
  - 2 engineers
  - 1 PhD student, with a fellowship
  - 4 technicians and administrative assistants
- Number of HDR : 4
- Number of PEDR : 1
- Number of "publishing" lab members : 6 out of 6

2 • Preparation and execution of the visit

10.00-10.30 : Meeting of the scientific committee alone, together with AERES representative

10.30-13.00: Presentation of the research activities and general presentation followed by 6 short scientific presentations (15 min each)

- Human marginal zone B cells
- KLHL6 and mouse B cell differentiation
- Mutagenic polymerases and immunoglobulin gene hypermutation
- In vitro affinity maturation of antibodies
- A new mouse model for studying B cell memory in the mouse
- Long-term B cell memory and conclusions.

13.00-13.30 : Lunch

13.30-14.00 : Discussion with institutional representatives

14.00-14.30 : Parallel discussions with (1) engineers and technicians; (2) PhD students/post-doctoral fellows; (3) scientists.

14.30-14.45 : Discussion with the director

14.45-16.00 : Committee members door-closed meeting

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

This research unit is a leading international research team focusing on B lymphocyte development and memory. The scientists are world leaders in the study of antibody diversification and, within the review period, have made pioneering contributions to the role of error-prone DNA polymerases in the process. Their other outstanding contributions have been to the study of B cell memory where they have pioneered the definition and characterisation of a new population of human B cells in which somatic hypermutation is proposed

to underpin antigen receptor diversification prior to antigen encounter. The unit has also made a very major contribution in this same period by way of identifying the spleen as an organ of central importance for the maintenance of long-term B cell memory.

The high status of the scientists in this unit is evidenced by the profile of their publications (*Immunity, J Exp Med, PNAS, Blood*…), their invitations to write reviews in prestigious journals (*Nat Rev Immunol, Annu Rev Immunol*) and speak at many major international meetings (Gordon conference, Keystone meeting, International Congress of Immunology, …) and by the high esteem with which they are held by their scientific colleagues worldwide.

The scientists in the unit have engaged in a judicious choice of scientific collaborations without losing focus in their own scientific endeavours. In addition to their productivity as reflected by their own scientific publications, the unit has translated its discoveries into intellectual property (5 patents) to develop and exploit hypermutating B cell lines. We note that such translation, whilst being pursued effectively, is (appropriately enough) not the dominant aim of the unit.

An additional strength of the unit is the impressively effective way in which they have taken advantage of their environment at Hopital Necker in order to interact with clinicians and make major advances in human B cell immunology by use of clinical samples. Indeed, one of the distinctive great strengths of this unit (in additions to its strengths in basic science and investigations in murine systems) is the facility with which the unit bridges the basic science/clinical science interface, by applying top quality, state-of-the-art molecular biology to immunological problems in man.

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

Molecular mechanisms of somatic mutations

During the assessment period, the unit has built on earlier work of their own and the Gearhart lab to provide definitive evidence for the central role of DNA polymerase eta in the induction of somatic mutation at A:T pairs, with polymerase kappa as back-up. This is excellent and highly important work on antibody diversification – which will go straight into textbooks. The unit has also made important contributions to the study of the involvement of low-fidelity polymerases in aspects of DNA repair (using mutant mice and cell-lines that they have created) as well as to the functions of polymerase mu and lambda (which they had identified) to V/D/J joining. Additionally, the group has published an important paper on the post-translational regulation of AID (a topic of importance to both immunology and cancer) and has exploited their proficiency in gene targeting in the BL2 line to develop a system for in vitro antibody maturation. These are all important achievements.

With regard to future work, their intentions to dissect the A;T phase of hypermutation are to be applauded. This is one of the major outstanding problems in antibody diversification and there are major (though difficult) issues here that need addressing: their resolution might give insight not just into antibody diversification but also into DNA repair in general. We hope that the lentiviral delivery/AID destabilisation strategies prove successful. But apart from these essentially genetic approaches, we wonder whether it would be worth also exploring investigations at the more biochemical level.

The diversity of B cell memory

In the past 4 years, the group has collected impressive evidence to support their original claim that IgM+IgD+CD27+ peripheral B cells, about 20% of the bloodborne B cells, are not classical memory B cells, as suggested by their expression of CD27 and their mutated antibody genes, but represent circulating marginal zone B cells with a repertoire diversified by somatic mutation outside of germinal centres, probably even independent of immune responses and early in life. This concept challenges classical views on the role and regulation of somatic hypermutation in man. It will require extensive further work to define the biology of this exciting B cell population, induction, place and timepoint of mutation, the mechanisms of maintenance, their role in immunity and immunopathology.

The analysis of this B cell population is reflecting an extraordinarily good interaction between clinicians and immunologists, a hallmark of this group. This interaction is also the basis of their more recent approach to analyse memory B cells generated in immune responses to smallpox (vaccinia virus) vaccination. They have identified the spleen as a major site of residency of such cells, while relatively few are found in blood. Upon splenectomy, circulating memory B cell numbers drop significantly. Vaccinia-specific memory B cells and memory plasma cells are independent populations in the memory phase. For further progress, it will be essential to develop techniques for the direct labelling of vaccinia-specific B cells. To complement this work, the group has now developed a murine "B cell memory reporter" mouse, in which the gene for green fluorescent protein is expressed upon AID induction. This is a very promising approach to dissect memory B cell diversity genetically and by adoptive transfer.

All of these findings are major contributions to our understanding of the biology of B cell memory. This is essential basic information with the possibility of a tremendous impact on applications such as vaccination strategies, and the treatment of allergy and autoimmune diseases, immunodeficiencies and lymphomas.

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

Excellent management of this small research unit : frequent lab meetings, journal clubs, all project leaders involved in strategic decisions, … No specific concerns.

6 • Recommendations and advice

— Strong points

High quality of science.

We were impressed by the quality of the younger research leaders. The unit should be proud that two young PIs trained in the lab have moved on to develop their own careers elsewhere. We congratulate the unit on the recruitment of a senior researcher from Pasteur Institute, who will be central to the B cell memory project. We wish the unit all success in completing this recruitment.

— Weaker points :

We were surprised by the relatively small number of junior researchers, i.e. graduate students and post-docs, in the unit, despite the excellent training and scientific environment provided. We were pleased to learn that the number of graduate students is soon to increase but remain concerned that funding constraints or concerns about upcoming dislocation caused by moving labs will make future recruitment of talented juniors more difficult.

— Recommandations :

We believe that, following the departure of one of the young team leader, the unit could benefit greatly from the recruitment of a biochemist. Such a biochemist could make a major contribution to the dissection of the mechanism of recruitment and function of DNA polymerase eta to the hypermutating IgV gene, as well as to the analysis of post-translational modifications of AID, which constitutes a particularly relevant topic in the study of B-cell lymphomagenesis.

Finally, we were concerned about the future plans for housing the unit. The hassle of relocation caused by dealing with the asbestos in the current building may well be an unfortunate but inevitable problem. However, uncertainty, excessive inconvenience and planning blight make recruitment of younger scientists difficult and adversely affect the future productivity of the unit both in the short and long terms.

Nevertheless, given that some dislocation is inevitable, one should consider relocation of the unit in an environment which brings together the leading groups at Necker. This INSERM unit boasts two of the international stars in the B cell immunology world. Given the excellence of their science, the proven quality of their interaction with clinicians at Necker and their ability to work productively with others to tackle major questions in human immunology, it becomes an exciting concept indeed if one imagines the possibility

that future rehousing could bring the multiple strengths in genetics and immunology at Necker together under one roof. We hope that the possibility of such relocation will be given very serious consideration.

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+	A+

UNIVERSITÉ
PARIS DESCARTES

Le Président
Axel KAHN

Paris, le 1er avril 2009

DRED 09/n° 128

Monsieur Pierre GLORIEUX
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport du comité de visite concernant l'unité « **UMR-S 783 Développement du système immunitaire** » rattachée à mon établissement.

Ce rapport n'appelle pas de commentaire particulier de la part de l'Université.

Je vous prie de croire, Monsieur le Directeur, à l'expression de ma meilleure considération.

Le Président de l'Université

Axel Kahn

Université Paris Descartes 12, rue de l'Ecole de Médecine 75270 Paris Cedex 06
Tél. 33(0) 1 40 46 16 01 Fax 33(0)1 40 46 16 43
Email : axel.kahn@parisdescartes.fr

Université Paris Descartes - Faculté de Médecine
Site Necker-Enfants Malades

Institut National de la Santé et de la Recherche Médicale

Unité INSERM 783

« Développement du système immunitaire »

Paris, le 27. 03 2009

We thank very much the members of the visiting committee for their very positive comments. Much effort has been devoted to the attraction of M2/PhD students, and we expect to have 3 PhD students next fall (at different stages of the diploma), and a fourth one in September 2010. We fully agree that the unit needs to recruit a biochemist (at post-doctoral level), and we plan to advertise this position, first toward the French scientific community, and, as soon as funding will be available, toward European post-doctoral candidates.

Claude-Agnès Reynaud
Directeur de recherche
Directeur INSERM U783

claude-agnes.reynaud@inserm.fr

tel : (33) 1 40 61 56 84 **156 rue de Vaugirard – 75730 Paris Cedex 15 (France)** fax: (33) 1 40 61 55 90