Cytokines, hématopoïèse et réponse immune

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

Cytokines, hematopoiesis and Immune response

University Paris Descartes

Mars 2009

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Cytokines, hematopoiesis and Immune response

University Paris Descartes

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 : Cytokines, hematopoiesis and immune response

Requested label : UMR CNRS

N° in case of renewal : 8147

Head of the research unit : Mr Michel DY

University or school :

University Paris Descartes

Other institutions and research organization :

CNRS

Date of the visit :

13th January 2009

Members of the visiting committee

Chairman of the commitee :

Mr Paolo DELLABONA, San Raffaele Scientific Institute, Milano, Italy

Other committee members :

Mr Clemens DAHINDEN, University Hospital Bern, Switzerland

Mr Christophe CAUX, Centre Leon Berard, Lyon

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

Mr Ulrich BLANK (CoNRS)

Mr Bruno QUESNEL (CNU)

Observers

AERES scientific representative:

Mr Marc BONNEVILLE

University or school representative:

Mr Bruno VARET, University Paris Descartes

Research organization representative :

Mrs Evelyne JOUVIN-MARCHE, CNRS

Evaluation report

1 • Short presentation of the research unit

- Number of lab members : 50 including
  - 9 researchers with teaching duties, all from the University Paris Descartes
  - 9 full time researchers, including 8 CNRS and 1 INSERM
  - 5 postdoctoral fellows
  - 11 engineers, technicians and administrative assistants
  - 16 PhD students, all with a fellowship
- Number of HDR : 12
- Number of students who have obtained their PhD during the past 4 years : 10
- Number of lab members who have been granted a PEDR : 0
- Number of "publishing" lab members : 17 out of 18

2 • Preparation and execution of the visit

10.00	Door closed meeting : committee members and AERES representative
10.15	Committee members, AERES representative, Unit's director
10.30	Overview Unit presentation (20 min.) (Unit's director)
10.50	Scientific presentations per thematic group (presentation by a member of the group and discussion with implicated researchers). (teams 1 to 5).
14.30	Meetings with staff members
14.30	Meeting with Researchers
14.45	Meeting with Engineers and Technicians
15 00	Meeting with post-docs and students
15.20	Discussion with CNRS, University Paris Descartes and IFR representative
15.40	Door closed meeting : committee members and AERES representative
16.10	Meeting with Unit's Director
16.15	End

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

The review panel unanimously agrees both on the high present quality and the future potential of the research Unit. The teams participating in the Unit have produced very solid science, publishing a significant number (112 publications in 2005-8 of which 41 with F/L authorship) of original and innovative concepts in top-notch journals that include Nature, JEM, Immunity, PNAS. More importantly, a search in Scopus, the largest abstract and citation database of research literature and quality web sources, shows the ever increasing rate of citations in the last four years for all the senior scientits and principal investigators affilated with this Unit. The same teams appear also very well integrated among them and with national research thanks to relevant numbers of *ad hoc* collaborations. Several international collaborations are also active on specific scientific issues. The Unit has filed a total of 4 patents and signed several research agreements with industrial partners. This definitively portraits a lively, stimulating, and productive Unit. All the research groups active in the Unit seem to take real advantage from the cross-fertilisation of ideas prompted by the different surrounding scientific perspectives and expetises. The added value of this is tangible in terms of originality in the scientific output.

The overall judgement is excellent.

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

Team 1: Cytokines at the interface between hematopoiesis and immune response.

This research group is composed of three senior scientists (1 DR1 CNRS, 1DR2 CNRS, 1 CR1 CNRS) including the director of the Unit. It has recently included a new senior investigator (CR1 CNRS) to further strengthen the research axis. Collectively, since 2005 this group has produced 42 publications (including the new investigator) inclusive of top-notch journals (J. Exp. Med and Immunity) and has filed one patent. The group has also been able to rise funding by establishing several industrial partnerships, which is an indication of the capacity of the group to attract, manage and exploit external investments.

This group can be considered as the driving motor of the Unit: 1) it performs highly original research at the interface between the immune and the hematopoietic system and 2) it fosters multiple intra- and extra-unit collaborations. Several projects have been developed during the past four years. They include the study of the role of the H4 receptor signaling in hematopoietic precursors in relation to cell cycle control and protection against the toxicity of anti-cancer drugs (patent). Another project focuses on the immunoregulatory role of murine basophiles. The group has identified a negative feedback control of basophile function by the monoamine transporter OCT3 as well as an important immunoregulatory function of IL-33 in shaping basophile numbers and Th2 cytokine production. Finally, they have shown that G-CSF growth factor signaling through Notch-Jagged 2 exhibits protection against experimental autoimmune disease by inducing tolerogenic Treg recruiting dendritic cells. This mechanism seems to be operative during autologous transplantation of G-CSF/Flt3 mobilized progenitors to prevent type 1 diabetes.

For the next 4 years, the group will continue to investigate the interplay between hematopoietic and immune system by pursuing: 1) The effects of conventional or new antagonists (in collaboration with industry) of H4R and of new putative H4R genes on cellular effectors of the innate and adaptive immune system; 2) The mechanisms that regulate basophil activation and their effects on the regulation of both the immune response and development of the hematopoietic system. The recruitment of a new scientist addressing the role of serotonin in a mouse knock out model will permit to widen the possibility of the group to study the role of biogenic amines in the immune activation and hematopoiesis. Furthermore the tolerogenic potential of mobilized hematopoietic progenitors will be further studied by defining inducing agents (i.e. TLR) as well as the responsible cellular and molecular mechanisms (NKT, DC subtypes). The research themes are quite original and concentrate on the function of yet ill-defined rare leukocyte subpopulations at the interface of hematopoiesis and immunoregulation. They integrate well with many projects of the other groups.

Regarding university formation, one of the team members actively participated in lecturing at different universities and the training of master and PhD students.

Overall, the committee rates this group excellent in terms of productivity, research originality as well as national and international visibility. The long-term visibility is reinforced by the integration of a new researcher.

Team 2: Cytokines, NKT cells and TLR in normal and pathological immune responses.

This research group is composed of two senior scientists (DR2 CNRS, CR1 CNRS). The projects pursued by this group are original, innovative, well focused and carefully planned. They have already produced remarkable results in the past 4 years, resulting in the delivery of new concepts in the field of innate T lymphocytes (such as the discovery of a NKT-17 subset, producing IL-17) and in 30 publications in prominent journals (including J. Exp. Med, PNAS.). The project proceeds along two main axes, that are very well integrated with each other: investigating the interplays between lipid-specific NKT cells, the best characterised subset of innate-like T lymphocytes, and the TLR-dependent stimulation by innate signals, and the result of their interactions in controlling the development of autoimmunity and asthma. The new set of results obtained so far, which will belong to the scientific production of the next 4 years, are extremely promising: they start to uncover new functions of NKT cells producing IL-17 and of MyD88-dependent signalling in relevant animal models of autoimmunity (IDDM), asthma and GvHD, coupled with smart connections to the corresponding human pathologies. Furthemore, this research group integrates well with the research aims of the other groups affiliated with the Unit, resulting in active collaboration on original ideas.

The senior scientists are actively involved in the training of 4 PhD students.

Team 3: Cytokines and virus in the regulation of the halthy and pathological hematopoiesis and immune system. Therapeutic applications.

This research group is composed of three scientists (2 CR1 CNRS, 1 CR1 INSERM) and 5 teacher-researchers (2 PU-PH, 3 MCU-PH) including the group leader. A new investigator (CR1 CNRS) has recently been recruited within the group illustrating the competitiveness of the team. Collectively, since 2005 this group has produced 25 publications and was associated to 22 additional publications through collaboration. In particular, they published 1 article in Nature, and filled one patent.

This group seems playing a growing importance within the Unit because of both the high quality scientific contribution and the research activity tightly connected to the medical needs.

Numerous projects have been pursued during the past four years: i) identification of a role of caspase 8 during erythroid differentiation, ii) identification of Neuropilin as a HTLV1 receptor, iii) study of the expression and the role of EBI3 and IL27, iv) identification of cKit mutation in mastocytosis and impact on treatment, v) identification of anti-transferrin receptor antibody (A24) as a potential therapeutic for HTLV-1 related Lymphoproliferations, vi) evidence for the role of pDC and Trail in the mechanisms of HIV infection induced CD4+ T cells depletion.

All these observations will be further extended in the future project. They will i) explore the role of HSP70 in the mechanisms leading to caspase 8 activation and protection from cell death during erythropoiesis, ii) extend the knowledge on Neuropilin and Semaphorin in immune regulation (role in GVL, on pDC, Treg…), iii) investigate the role of pDC in the in physiopathology of HIV and HTLV-1 infections and pharmacological interventions, iv) pursue the physiological role of EBI3, IL27 and IL35 in normal and pathological conditions (B cell malignancies). Finally, in connection to these fundamental research objectives, they are pursuing more translational objectives: i) identification of targets in wild type cKit mastocytois, ii) development of treatment in HTLV-1 related lymphoproliferation, iii) search of therapeutic target in the innate immune mechanism involved in the physiopathology of bone marrow transplantation.

Although most of these research axes are progressing and yeilding interesting observations that may result in therapeutic applications, most of them appear as quite independent line of research. Although the committee acknowledges the high level of scientific contribution and the originality of the concepts developed in the group, it also needs to alert the group leader that the diversity of the topic develop may became a real issue with a risk of dispersion and loss of scientific focus.

Furthermore, the group has been able to sucessfully combined the study of fundamental immuno-hematological questions with clinical research in patients. The committee also feels that this clinically oriented group could play a more important role within the unit by fostering the translational aspects of some projects of groups I and II, which do mainly pre-clinical research, particularly since there is a considerable overlap of interests (e.g. in hematopoiesis, pDCs, Tregs, IL-12-family cytokines).

Regarding university formation, 12 PhD students have graduated or are under formation within the group.

Team 4: Normal and pathological lymphoid differentiation

This group is composed of one Professor and four assistant-professors of hematology belonging to the University and hospital. It has not yet officially joined in the UMR8147 and its research activity is mostly done in the Laboratory of Hematology at Necker Hospital. Past activities have focused on T-acute lymphoblastic leukemias and more specifically on their classification according to TCR genotyping. The group cloned also several translocations in lymphoid malignancies in the past. However, the main contributor to this latter activity moved to Institut Gustave Roussy, explaining why the group wants to join UMR8147. The scientific output in the last four years is quite good, achieving the top journals in the field (three publications in Blood several in Leukemia).

The group pursues translational projects and the scientific rational for joining in the UMR8147, which is mainly focused on fundamental research, is to explore in lymphoid malignancies some mechanisms identified in normal lymphoid physiology.

This committee considers that, on the one side, the merging of this research group in the UMR8147 might have a positive impact on the overall strategic plans because of :

- Good and long-lasting collaborations with large clinical study groups in the field of acute lymphoid leukaemia
- Sharing of technical facilities used for routine diagnosis
- Excellent experience in hard core genomics technology and in rare lymphoid diseases
- Common scientific interest for the patho-physiology of lymphoid cell development between UMR8147 and this group

On the other side, however, the committee identifies some problems that must be avoided in order to maximize this integration process:

- This research group will be physically separated from the UMR8147. This suggests that people from this group will have to be proactive to interact with the partners at UMR8147;
- Although potentially promising, projects connecting basic and translational research seem not yet clearly defined.

The main risk is that this group would not find interactions with UMR8147 and continue their own independent research, which is productive yet it would not provide the much wanted reciprocal benefit to both partners in the joint venture. A way to avoid this could be to define a common project as soon as possible.

Team 5: CNRS-FIOCRUZ International Associated Laboratory. Cytokines, thymus and cell migration

This group represents a French-Brasilian join venture between CNRS and the Fiocruz (Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Rio de Janeiro). The French representative is at the UMR8147, and it is composed by two senior scientists (DREm INSERM, DR2 CNRS). This international research group has a dedicated budget from independent funds. The research project centre on the study of mechanisms regulating migration in relation with thymocyte development in NOD mice, a pre-clinical model for type I diabete, or human T-Acute Lymphopcytic Leukemia. The projects investigate the role for the Neuropilin/Semaforin interactions in several aspects of T-ALL biology, and of CCR7, CCR9 and thei ligands in the altered migration of NOD thymocytes. Both project integrate well with the other ongoing projects in the Unit.

The added value for the research unit of this international project would consist in the exchange of post-docs and students with Brazil, that seem essentially to operate from Brasil to France, and in the development of joint research projects.

Because the international laboratory is independently funded, and therefore it is not a financial burden for the research unit, and in the light of the fact that this laboratory brings young potentially good scientists from Brasil to Paris, the evaluation committee considers this initiative a possible advantage for the research unit.

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

In general, the research unit seems fairly well equipped for its research needs. There are however two problems concerned with the infrastuctures of the research unit :

- The lack of space, which may impact negatively new recruitments, which are vital to guarantee the ever increasing productivity of the research unit;
- The animal facility, which is obsolete for the actual use, particularly in terms of barrier to contaminations, and makes the work difficult. Therefore, while waiting for the construction of a new dedicated structure, the evaluation committee endorses the research unit's request for the acquisition of ventilated racks (500 k€) that would improve greatly the health of animals and improve the working efficiency for the time being.

The working atmosphere in the research unit appears fine: the governance of the research unit is based on a decision-making process that is shared by the Director and the senior scientists. This seems to have established a factual collaborative attitude among all the members of the Unit, which includes also the participation in a common fund generated by devolving a fixed percentage of private grants obtained by each research group or scientist, which is used to cover common needs.

The administrative/technical personnel employed in the Unit pinpoints the necessity to solve their "lunch problem" through a convention between the different partners.

6 • Recommendations and advice

- Strong points :

All members of the committee unanimously agree on the overall excellent quality of the Unit. The projects performed in the Unit are all innovative, some even flamboyant, and tackle a wide range of biological problems encompassing different relevant topics in immunology and hematology. This wide spectrum of scientific interests is a positive characteristic specific of this Unit and clearly fosters a relevant cross-fertilisation among the participating laboratories, resulting in the proposal of orginal hypothesis to pursue.

The research unfolds well along the two bench-bed side-bench polarities, leading to both the clinical transfer of the findings and products of the basic and pre-clinical research, and the investigation of specific human immunological or hematological pathological conditions as models from which are raised new hypothesis on mechanisms.

The committee considers also very positive the management/governance of the Unit, which follows a bottom-up approach in which all the PIs participate in the strategic decisions, as well as in the generation of a common fund to manage at least part of the running costs for common utilities.

The senior scientists and project leaders are all capable and have shown to possess a clear vision for future directions. The committee has also noticed a second line of young promising scientists, who have displayed a good deal of scholarship and leading capacity.

- Weak points :

The very same wide range of scientific interests and projects that characterise this Unit should not become a burden due to dispersion and loss of scientific focus. Care should be taken to prioritise the most promising research lines vis a vis their ultimate relevance for fundamental biology or pathophysiology of the immune system and hematopoiesis.

- Recommendations :

We recommend the Director and the project leaders to watch over possible loss of focus, and eventually prioritise the projects they are undertaking.

Moreover, it is fundamental to continue to invest in young investigator and nurture the ones already active in the Unit in order to guarantee a future turnover of group leaders.

We feel the proposed joining of team 4 in the unit should reflect not just a strategic decision but also, and especially, a real scientific need for the research unit, which should require the expertise of the joining laboratory to implement a specific area of research.

We also recommend to keep for the future the good balance between basic and translational research, as it is performed now, and avoid possible drift towards a prevalent clinical-transational type of investigation.

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 7 avril 2009

DRED 09/n°124

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 8147 Cytokines, hématopoïèse et réponse immune** » 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

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CYTOKINES, HEMATOPOIESE ET REPONSE IMMUNE
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Réponse au rapport

We have read the report of the visiting committee attentively and appreciated its overall conclusions. We are actually aware of the possible risk of dispersion and loss of scientific focus in the future, pointed out by the members of the evaluation board and are ready to take their recommendations into account, especially by reinforcing the bilateral exchange between the scientists and students located in the Sevres building (teams 1, 2, 3 and 5) and the Pasteur tower (team 4).

Paris, April 6, 2009

Dr. Michel DY

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