Cytokines, chimiokines et immunopathologie

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

Cytokines, chemokines and immunopathology

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 :

Cytokines, chemokines and immunopathology

University Paris 11

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

mars 2009

Evaluation report

The research unit :

Name of the research unit : Cytokines, chemokines and immunopathology

Requested label : UMR_S INSERM

N° in case of renewal : U764

Head of the research unit : Mr Dominique EMILIE

University or school :

University Paris 11

Other institutions and research organization:

INSERM

Dates of the visit :

November, 18-19 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

Mr Pedro ROMERO, LICR, Lausanne, Switzerland

Mrs Angela SANTONI, University of Roma, Italy

Mr Frank TOLEDO, University Paris 6, France

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

Mrs Valérie PARADIS, University Paris 7, France

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

Mrs Danila VALMORI, Nantes, CSS INSERM representative

Mr Jean-Paul FERMAND, Paris, CNU representative

Observers

AERES scientific representative:

Mr Nicolas GLAICHENHAUS

University or school representative:

Mr Claude BOUCHAIX, University representative

Mr Jacques BITTOUN, University representative

Research organization representatives :

Mrs Marie-Josèphe LEROY-ZAMIA, INSERM representative

Mr Eric SOLARY, Institut Gustave Roussy representative

Evaluation report

1 • Short presentation of the research unit

- Number of researchers with teaching duties : 14
- Number of full time researchers : 5
- Number of engineers, technicians and administrative assistants : 15
- Number of PhD students : 30

- Number of students who have obtained their PhD
- Average lenght of PhD during the past 4 years: 8
- Number of HDR: 10
- Number of PEDR : 2
- Number of “publishing” lab members: 19 out of 19

2 • Preparation and execution of the visit

Day 1

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

Time : from 11 :30 to 12h00
Time length: 30 minutes including questions
Presentation by the head of the unit : past activity and projects

Time : from 12 :00 to 13 :00
Time length: 60 minutes including questions
Presentation by the leader of team #1: past activity and projects

Lunch from 13 :00 to 14 :00

Time : from 14 :00 to 15 :00
Time length: 60 minutes including questions
Presentation by the leader of team #2: past activity and projects

Time : from 15 :00 to 16 :00
Time length: 60 minutes including questions
Presentation by the leader of team #3: past activity and projects

Coffee Break from 16 :00 to 16 :30

Time : from 16 :30 to 17 :30

Time length: 60 minutes including questions

Presentation by the leader of team #4: past activity and projects

Time : from 17 :30 to 18 :30

Time length: 60 minutes including questions

Presentation by the leader of team #5: past activity and projects

Day 2

Time : from 8 :30 to 9 :00

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 9 :00 to 9 :30

Time length : 15 minutes

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

Time : from 9 :30 to 11 :30

Time length : 120 minutes

Door-closed meeting : Committee members, AERES representative

Time : from 16 :30 to 17 :00

Time length : 30 minutes

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

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

The research unit has worked, during the last four years, on various aspects of cytokines, chemokines and immunoregulation. One of the major axes concerned the study of glucocorticoid induced leucine zipper (GILZ) that imparts a tolerogenic activity on human dendritic cells. The more historic activity on chemokines was continued by studying its involvement in ovary cancer, in pulmonary arterial hypertension, and in liver inflammation. Well-integrated experimental models and clinical research have led to very intriguing results published in numerous highly cited papers in good to top-level specialty journals.

This research unit will undergo major reorganization and will consist of five teams working on the physiopathology of immunological and inflammatory disorders. New teams, working on allergy, Myasthenia Gravis, and immunodeficiency disorders will join the unit or individualize from preexisting groups. Promising young researchers will thus emerge and be allowed to lead independent, but well integrated, research projects. The current group working on pulmonary hypertension will found a new research unit.

Importantly, GILZ provides a central axis and several groups will address its role in distinct pathologies. Another common interest of the unit's laboratories concerns the role of chemokines in immunopathology. The committee also noticed an excellent complementarity of newly developed animal models, *in vitro* systems, and clinical research. The proposed projects, ranging from strong basic research to clinical studies on intriguing,

important, and/or emerging pathologies, should lead to important breakthroughs with strong potential for translational impact.

The panel appreciated the excellent involvement of the unit-director as well as of several of its present and future members in teaching, in scientific politics of the university and well beyond, and in national and international networks.

A note of concern relates to the fact that several of the unit's technicians will retire soon and that it heavily depends on contract-technicians. The panel recommends that supporting institutions pay particular attention to this issue.

Finally, the personnel of the unit (students, postdocs, technicians, staff scientists) acknowledged the charisma and dedication of the unit's director.

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

Team 1 :

This research team has made the major scientific contribution of discovering the glucocorticoid induced leucine zipper (GILZ) protein as an important regulator in tolerogenic dendritic cells (DC). Importantly, GILZ expressing cells induce Foxp3-expressing regulatory T cells, potentially opening therapeutic applications in the management of autoimmune disease. A very original aspect of the past research activity concerns the effect of activated mast cell-products on GILZ expression in DCs. The required in vivo verification experiments are addressed in the research project. The past research activities of this team also included high quality work on the role of chemokines in ovary cancer and on the effects of type I interferon administration on primary immune responses to HIV infection.

The scientific production of this team in the last four years is very solid. However, whereas the impact factor of the journals in which the very interesting results were published is medium high, the panel was somewhat disappointed that they were not published in higher impact factor journals. The experimental plan on genetically engineered mouse models should allow for such type of publications.

The team has made the strategic decision to switch, temporarily, entirely to experimental research. The committee considers this decision entirely justified since it will without any doubt lead to excellent science. Of note, with its considerable clinical expertise, the team will be able to validate its fundamental findings in clinical settings in the future. The research project for the next four years appears feasible and concerns identification of ways to modulate GILZ expression for future clinical application as well as development of genetically engineered mouse models for the study of GILZ in immunopathology. The committee would recommend that the team also addresses the functional activity of other GILZ family members. Overall the project is highly original, with cutting edge tools being developed. Despite the fact that it is working in a very competitive field, the team is in an excellent position to make original and important contributions. It will also have the opportunity to develop fruitful collaborations intramurally, in France, and at the international level.

Nom de l'équipe : Dendritic cells, mastocytes and immune tolerance

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+

Team 2 :

This team will join the research unit in 2010. The team focuses on innate cell signaling in immunotoxicology and immunopharmacology, and has firm roots in pharmacology and a strong tradition in occupational asthma. The past work has demonstrated a number of very interesting signaling pathways triggered in dendritic cells (DC) by chemical sensitizers that cause allergy. Importantly, the group has demonstrated direct activation of DC by chemical allergens, mediated by the NRF-2 pathway. Another strong point is the elucidation of bidirectional DC-neutrophil interactions, potentially involved in regulation of hypersensitivity. The members of this future team have published their very interesting results in good level specialty journals. Moreover, they are heavily involved in teaching activities.

The research project proposed concerns further analysis of signaling pathways involved in DC activation by chemical sensitizers (e.g. Nrf-2), the molecular mechanisms of bidirectional DC-neutrophil interactions, and the roles of FOXO factors and GILZ in modulation of signaling pathways in neutrophils. This part of the future work, which is in general a logical extension of the prior work and of high quality, is somewhat risky, but has the potential of a major breakthrough.

The committee notices that for part of the planned work there is heavy dependence on a single cell line to study neutrophil biology. It recommends validation of results with fresh neutrophil granulocytes. Also, hard data are needed on in vivo relevance of DC/neutrophil interactions. It seems to the panel that the substantial expertise in granulocyte biology would become more fruitful with a full-time scientist employed in this area.

In conclusion, the committee considers this team scientifically very coherent and solid. It will substantially contribute to the scientific activity of the unit with its expertise in signal transduction. The scientific coherence of the future team with the rest of the unit is best illustrated by the strong collaboration it will develop with team #1. Its localization in the pharmacy faculty is a plus because it strengthens the interactions between the faculties of medicine and pharmacy and should not pose problems because of the scientific coherence with the rest of the unit.

Nom de l'équipe : Mechanisms of signalling in innate immune cells in immunotoxicology and immunopharmacology

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	A	A+	B

Team 3 :

The objectives of team 3 are dedicated to the understanding of the mechanisms of recruitment and activation of inflammatory cells into the liver in alcoholic and non-alcoholic liver diseases. The project is based on previous results recently obtained by the group, showing the involvement of (1) specific abnormalities of lymphocytes in obese mice, (2) GILZ (glucocorticoid-induced leucine zipper) as a key-contributor in liver inflammation in alcoholic hepatitis. Despite a short track record, the results of this team were published in top-level specialty journals.

In the setting of non-alcoholic hepatitis, the group will aim to investigate the importance of the recruitment of macrophages into the liver and evaluate their state of activation using animal models and in vitro experiments. Since they observed a role for GILZ in liver inflammation, they will aim to assess whether liver macrophages are able to produce GILZ and investigate the functions of this protein by modulating its expression in vitro. The relevance of GILZ will be also verified in humans on liver biopsies obtained from obese patients. In the setting of alcoholic liver disease, the role of GILZ in macrophage accumulation in the liver will be investigated using two pertinent animal models. Finally, relationships between GILZ expression-levels and clinical outcome and prognosis of patients with acute alcoholic hepatitis will be evaluated.

The project is original, dealing with an emerging and competitive topic, especially in the context of obesity, the incidence of which is growing worldwide. For that purpose, several relevant animal models have been developed and members of the group have a high level of expertise in the pathophysiology of the liver diseases. Collaborations with other teams of the unit will provide significant synergy, especially regarding the field of GILZ. The good interactions of this team with the clinic will allow for verification of the validity in Man of experimental data obtained. The panel recommends that priorities in the different parts of the project be clearly defined. The up-coming results will have high potential for valorization and development of partnership with industry for drug development.

In conclusion, this team is a leader in animal models of liver inflammation and has developed excellent complementarity with clinical studies. Its scientific activity perfectly integrates in the research unit. However, the committee noticed the absence of required technicians dedicated to this relatively small team.

Nom de l'équipe : Inflammatory response in non alcoholic fatal liver disease

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	A	B	NN	B

Team 4 :

Research in this team focuses on the analysis of immune dysregulation in Myasthenia Gravis (MG). The group was the first to report a functional defect of CD4+CD25+ regulatory T cells (Treg) in MG. It also characterized chemokine, acetylcholinesterase, and estrogen expression in MG (and control) thymi. These results were published in good to top-level specialty journals. Of notice, one of these papers is very highly cited.

This team will join the research in 2010. Its activity on immune-dysregulation will make it a very coherent part of this unit. The proposed project focuses on the causes and consequences of Treg-functional defects, using global approaches and also investigating isolated specific observations. The role of chemokines, angiogenesis, and estrogens in MG will be further investigated using, among others, novel mouse models. Finally, molecular mechanisms involved in muscular dysfunction in MG will be studied.

Because of the access to unique patients' material, including peripheral blood and thymic specimens from MG patients, the group is in an ideal position of leading research in the field. It is indeed involved in and directs international networks. In addition, the committee was impressed with the potential of new interesting mouse models developed by the group. Whereas the translational aspects of the research are excellent, it was felt that most of the past studies on the defects of Treg in MG were descriptive and not mechanistic. Moreover, they did not focus on antigen-specific immune responses, such as those directed against AChR, which represents an almost unique but missed opportunity. In sum, the committee supports the studies presented in the research project, but strongly recommends focusing on studies addressing the molecular and mechanistic bases of Treg dysregulation in MG in the context of antigen specific immune responses.

Nom de l'équipe : Pathological and regulatory mechanisms in myasthenia gravis

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 5 :

This new team results from the association of the team leader who joined the research unit in October 2007, with a CR1 CNRS, who worked in previous team 1. In addition, it will be composed of one PU-PH, one CCA and three technicians hired on research contracts.

The team leader is a young scientist who was recruited as CR1 at INSERM in 2007. As a postdoctoral fellow in the Pasteur Institute, he worked on chemokines, particularly on SDF-1/CXCL12. He identified a second receptor for CXCL12, CXCR7 and he characterized the regulation mechanisms of signalling and intracellular trafficking of its other receptor, CXCR4. The latter work resulted from the study of the rare inherited human immunodeficiency syndrome WHIM, which is characterized by a gain of CXCR4 function. In addition to this major contribution, K.Balabanian made very important observations about a second form of human immune deficiency, the idiopathic CD4+ T cell lymphocytopenia (ICL), in which he identified a defect in CXCR4 expression at the surface of CD4+ T lymphocytes. Between 2003 and 2008, the team leader published seven articles in good to top impact factor journals.

During past years, one of the team members has mainly worked on SDF-1/CXCL12 expression by malignant cells and reported a critical role for this chemiokine in ovarian tumour angiogenesis and progression.

Team 5 will extend the previous studies on the role of SDF-1/CXCL12 in human disorders. Genetic and molecular bases of CXCR4 dysfunctions in WHIM syndrome will be studied using a novel mouse model. This pre-clinical model will also allow selecting antagonists specific for CXCL12 or CXCR4. Regarding ICL, team 5 projects to determine the mechanism of defective CXCR4 expression and to identify and validate candidate genes in mouse models. It will also study the contribution of the two CXCL12 receptors to development of epithelial ovarian tumours.

The committee was very favourably impressed by the presentation made by the team leader. All its members considered that this new team is composed of young scientists who are continuing a very original and exciting line of research. This research has already produced excellent results including a major breakthrough in the physiopathology of the WHIM syndrome and important observations in another rare human immunodeficiency, the idiopathic CD4+ T cell lymphocytopenia. By further studying these diseases, using appropriate means (including an excellent mouse model of the WHIM syndrome), team 5 is likely to continue to provide important insights into the molecular regulation of T cell migration. The ability to study the role of CXCL12 and its receptors both in immune deficiencies and in malignant disorders, namely in ovarian tumours, represents another strength of the project.

Nom de l'équipe : The chemokine SDF-1/CXCL12 and its receptors in Immunopathology

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	NN	A

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

The unit's groups have acquired appropriate levels of funding for their research. The personnel of the unit acknowledged the charisma and dedication of the director. Given the reorganization of the unit, with a group from the faculty of pharmacy becoming part of it without leaving its current premises, it will be important to fully integrate all members by continuing the current regular meetings.

6 • Recommendations and advice

— Strong points :

Very strong implication in teaching, scientific politics, and networks.

Strong thematic coherence.

Good hiring of young scientists.

Publications in good to top-level journals.

— Weak points :

Too strong dependence on contract technicians.

— Recommendations :

It will be important to replace retiring staff technicians.

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-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 7 avril 2009.

N/Réf. : 101/09/GCo/LM/LS

Objet : Rapport d'évaluation d'unité de recherche
N° S2100012401

Monsieur le Directeur,

Vous m'avez transmis le dix neuf mars dernier, le rapport d'évaluation de l'unité de recherche « Cytokines, chimiokines et immunopathologie » - UMR S 764, 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 Dominique EMILIE, Directeur de l'unité de recherche.

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

Guy COURRAZE
Président

UNIVERSITE PARIS-SUD 11 - Présidence - 91405 ORSAY CEDEX

P.J. : Commentaires de Mr EMILIE

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Institut Paris-Sud Cytokines
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Directeur: D. Emilie

Responses to remarks of the AERES Visiting Committee

March 27, 2009

We thank the Visiting Committee for its comments and suggestions, regarding either scientific aspects of our program or organization considerations. Basically, we agree with Committee's report, and we will elaborate only on a few specific points.

Points linked to the institute policy.

- Minor comment: fortunately, the average length of PhD thesis in our Institute is not 8 years, as stated in the report.

- We appreciate Committee encouragements to develop further experimental in vivo models of human physiology and disorders. This has been during the last 4 years a strong investment for a laboratory totally dedicated so far to human immunology. Now, most projects associate studies of murine models and of clinical samples. As noted by the Committee, this dual approach will enable us to better figure out molecular and cellular mechanisms involved in immunopathology, and our expertise in human immunology and clinical trials will then allow us to extend these conclusions to the human condition, and possibly to the care of patients.

- We also appreciate that the Committee considered favorably the joining into this common project of scientists from different origins and experiences, located on two different sites. We feel that integration of all members of our program will be easy, as all of them have already been working together in the recent past, either for scientific, educational, hospital or university projects. The coherence of our general scientific project and the complementary experiences and knowledge of laboratory members, both underlined by the Committee, make us quite confident on our ability to even reinforced already ongoing collaborations. We feel that this integration will go far beyond regular meetings between all members of the laboratory, and will include common projects shared between teams.

- We share with the Committee its worries regarding our strong dependence on contract technicians, which will even increase with the imminent retirement of several INSERM technicians and engineers presently affiliated to our laboratory. The Committee point out the lack of technician dedicated to team 3. We indeed regret this situation, but we also hope that it will not become the rule for the next years, as 3 of the 5 teams of our institute (teams 1,3 and 4) will be without any technician/engineer on a permanent position by the end of 2010, unless receiving an urgent and strong support from our "tutelles".

Points linked to research teams

Teams 1,2,3,5: no specific comments.

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Team 4.

Team 4 would like to thank the reviewers very much for their comments and advices on the Treg cells. We understand the Committee's concern that antigen-specific Treg cells should be investigated and, indeed, we already started a collaboration with the team of Prof. Sara Fuchs (Weizmann Institute, Israel) to develop a therapeutic approach based on antigen-specific Treg cells. Analysis of Treg defect mechanisms is obviously a major issue. As presented, we have already shown that thymic epithelial cells are implicated in this defect, and our ongoing project aims to explore the molecular mechanisms involved.

We would like to underline that research lines of major importance to understand the etiology and pathophysiology of MG are also being pursued. For example, we demonstrated a role for CXCL13 (Meraouna et al Blood, 2006) and CCL21 (Berrih-Aknin et al, Ann Neurology, in press) in the development of thymic hyperplasia, and new transgenic mouse models are under construction to validate the in vivo role of these chemokines in B cell migration to the thymus. The data we presented on the high expression of interferon-alpha-regulated genes in MG patients' thymus and on the striking effect of poly (I:C) on AChR expression support a viral etiology, whose mechanisms leading to thymic hyperplasia are now being addressed.

Finally, we would like to emphasize the international recognition of our team. Indeed, the two current European projects on MG, one in basic science (FP6 program, 10 teams) and another in Public Health (50 teams of Scientists, clinicians and associations of patients), are coordinated by our team. In addition, our team coordinated another project in the FP5 program and obtained a NIH grant as principal investigator.

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