Physiopathologie et biothérapies des maladies inflammatoires et autoimmunes

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Pathophysiology and biotherapy of inflammatory and autoimmune diseases

From the

University of Rouen

INSERM

December 2010

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et de l'enseignement supérieur

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

December 2010

Research Unit

Name of the research unit: Pathophysiology and biotherapy of inflammatory and autoimmune diseases

Requested label: UMR_S

N° in the case of renewal: U905

Name of the director: Mr Olivier BOYER

Members of the review committee

Committee chairman

Mr Roland, LIBLAU, University of Toulouse 3, Toulouse

Other committee members

Mr Bruno DEBETS, Erasmus Medical Center, Rotterdam, The Netherlands

Ms Dominique KAISERLIAN, University of Lyon 1, Lyon

Mr Hans YSSEL, University of Paris 6, Paris

Ms Valérie ZIMMERMANN, University of Montpellier 1, Montpellier

Mr Bertrand DUBOIS, University of Lyon 1, Lyon (CSS INSERM member)

Observers

AERES scientific advisor

Mr Paul HOFMAN

University, School and Research Organization representatives

Ms Christine TUFFEREAU, INSERM

Mr Cafer OZKUL, University of Rouen

Report

1 • Introduction

- Date and execution of the visit

The site visit of the Rouen Inserm U905 took place on December 2nd, 2010. The evaluating committee evaluated the 2 teams together, but were divided in 2 groups to discuss with either students or technical staff. Committee members collaborated closely to prepare the final report.

The committee had sufficient time to listen to presentations, assess the research of the teams, assess the environment for the PhD students and technical staff as well as having the needed discussions afterwards. At the end of the 2 teams' presentations, an in-depth discussion among panel members took place to summarize salient issues, exchange views and organize the preparation of the final report.

- History and geographical localization of the research unit, and brief presentation of its field and scientific activities

The Inserm unit 905 (Physiopathology and Biotherapy of inflammatory and autoimmune diseases: Director Olivier BOYER) started in 2008, and continued the research efforts of the former Inserm Unit 519 ("Defense proteins involved in inflammatory immune responses") headed by François TRON at the University Hospital Centre in Rouen. Originally, the three fields of research of U519 were: (1) hepatic proteins in the systemic inflammatory response syndrome; (2) complement and tissue physiopathology; and (3) auto-antibodies in specific and nonspecific autoimmune organ disease with emphasis on hepatomas, cancer, disorders of the central nervous system and autoimmune diseases, such as pemphigus, lupus and rheumatoid arthritis.

Initially created as an Avenir team (Fundamental immuno-myology and biotherapy), integrated into the IFR 23, U905 has expanded its manpower and scientific goals and built on the scientific and clinical "history" of the previous Unit. Presently, U905 consists of 45 persons divided into two teams. It is affiliated to the Inserm ITMO "Immunology-hematology-pneumology" (IHP) that encompasses the field of biotherapies.

The overall objectives of U905 relate to basic research studying the molecular mechanisms that underlie the regulation of normal and pathological immune responses as well as translational research that includes clinical studies in the field of inflammatory and autoimmune diseases of the locomotor apparatus and the skin. The latter project is one of the strategic axes of the Teaching Hospital Institute of Biomedical Research (IHURBM) at the site of Martainville.

Team 1

" Physiopathology and biotherapies of immune pathologies of locomotor apparatus" includes the group of rheumatologists of the Unit and is headed by Olivier BOYER and Michel SEMAN. Their main research efforts focus on (i) the identification of novel physiological and physiopathological mechanisms of autoimmune regulation in myositis by developing and studying experimental mouse models of auto-immune myositis, as well as on (ii) the biology of regulatory T cells and in particular the immunoregulatory role of ectonucleotides. Furthermore, the team conducts clinical studies in the field of myositis and rheumatoid arthritis. Their work has led to the development of a novel transgenic mouse model that is used to study the molecular mechanisms of tolerance towards muscle-expressed autoantigens, to the demonstration of the role of ectonucleotides in the homeostasis of regulatory T cells, to the identification of prognostic and drug-responsiveness biomarkers in rheumatoid arthritis, as well as novel diagnostic tools in inflammatory myopathies.

Team 2

"Physiopathology and innovative therapies of immuno-dermatological diseases", directed by Philippe MUSETTE, studies the physiopathological mechanisms of autoimmune dermatological disorders and drug-induced toxidermia through experimental models and clinical studies in collaboration with the Reference Center of bullous cutaneous autoimmune diseases directed by Pascal JOLY. The research of this team focuses on the understanding of the role of T cells in drug-induced eruptions and viral reactivation on T cell activation, as well as the analysis of Toll-like receptors and their implication in the development of the autoimmune B cell responses in lupus erythematosus. Finally, the team has conducted biological and clinical studies to assess the efficacy of an anti-CD20 monoclonal antibody in the treatment of patients with pemphigus.

Overall, the Unit makes extensive use of current technologic approaches, such as transcriptome and proteome analysis, and carries out innovative diagnostic and theranostic research, which is guided by the results from cellular and genetic therapies.

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	11	9
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	4	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	11	8
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	4	
N6: Number of Ph.D. students (Form 2.7 of the application file)	8	
N7: Number of staff members with a HDR or a similar grade	9	7

2 • Overall appreciation on the research unit

• Summary

The research unit 'Pathophysiology and biotherapy of inflammatory and autoimmune diseases' studies the immune response and its regulation in health and autoimmunity, in particular in autoimmune and inflammatory disorders affecting muscle, joint and skin. In addition to the increase in the understanding of these pathologies, research aims at improving diagnosis and therapy. The unit comprises two teams: (1) the BOYER team that focuses on muscle and joint; and (2) the MUSETTE team the research of which is centered on skin. The teams are building on high risk/high gain projects. This has worked very well and has led to highly original results and novel concepts. The teams are primarily committed to clinical questions and therefore the impact of their work is beyond doubt. Appreciations of each team are given in the section 4.

Science, management, as well as the social and scientific atmosphere, are very good, which, by and large, is the result of the enthusiasm and commitment of the director. The long-term vision of the unit is to excel in basic and translational research with respect to autoimmunity or chronic inflammatory diseases affecting the three above-mentioned organs. The committee members consider this an important goal for which there is a clear and non-occupied niche at the national as well as international level. The proposed reorganization of the unit for the next five-year period, i.e., focus of the BOYER team on muscle and focus of the MUSETTE team on both joint and skin, is anticipated to represent a better strategy to reach this goal. Teams will be better-focused and balanced with respect to size and resources. In the future, the dynamics of this unit, good level of publications, space availability and strong support by the university should allow attraction of new additional high profile investigators.

The research unit is well embedded in the infrastructure of the University of Rouen and takes advantage of the excellent organization of the IFR in different facilities with the mutualization of human resources. The output of the unit is graded as very good with recent publications in J Exp Med and Sci Transl Med. Also the valorization is graded as very good, with patents with respect to a diagnostic gene set and a quantitative assay for autoantibodies for myositis, as well as gene sets predicting responses towards anti-inflammatory drugs in the setting of arthritis. Provided the recent upward momentum is maintained, it is anticipated that the international recognition of this research unit will further increase. One minor point of caution is a tendency to over-emphasize the value of preclinical models that do not, in all cases, have proven clinical relevance. The committee feels that the research unit is well on its way to become a center of excellence, and that it may benefit from one or several full-time researcher(s) with a permanent position at an associate professor level to reinforce the existing teams and contribute to the clinical validation of the results obtained in their mouse models or to lead to the emergence of a third team (i.e., each team covers the studies on a single organ).

• Strenghts and opportunities

The Unit performs excellent translational research in autoimmune processes affecting the muscle, the skin and joints. There is no doubt, when considering their past and present achievements, that they conduct very good basic and clinical research and that they are clearly undertaking projects of excellence in the three fields. This is also highlighted by recent major publications in top international journals, strong patents as well as by strong financial support from both institutional and industrial partners.

The research strength of the unit is supported by the clinical origin of the 2 team leaders, their involvement in pathophysiological research via commitment and skills to develop relevant physiopathological animal models reproducing human diseases (Team 1, O. BOYER). The presence of many clinicians with robust knowledge of human immunology and the commitment to physiopathological and clinical research are emphasized by the originality and pertinence of the projects for the diagnosis and treatment of autoimmune diseases.

Both teams benefit from access to large and well-diagnosed patient cohorts, both through local hospital departments and via international collaborations and have good access to technology platforms in the IFR.

The unit has many preclinical models in place, and the projects of both teams are well defined and fill a niche in French and outside French research.

Both teams provide good mentoring of PhD students.

- Weaknesses and threats

The teams are not yet fully internationally recognized, most likely because the field of myology is only beginning to emerge and because DRESS represents a rare disease, with only a small number of lab involved at the international level.

The unit does not have a full time researcher. Although many clinicians working in the unit (both Team 1 and 2) are very committed to research (both fundamental and clinical research) and fulfill top level student and PhD trainings, their teaching and clinical duties may hamper participation at prestigious meetings and joint lab meetings.

- Recommendations

Given the quality of science conducted in the Unit, the well-recognized expertise in clinical immunology of the 2 PIs at a national level, the good and well organized collaboration between people, it is anticipated that the Unit should benefit from full time researchers. One way to achieve this goal, and at the same time strengthening the Unit's international visibility and attractiveness to young researchers, would be via the organization of an International course on human Immunology research and/or organizing a conference on Autoimmunity.

Organize regular joint lab meetings to maintain the scientific discussion and social network between the 2 Teams. In addition, maintain good communication, quality of work and collaboration by a yearly retreat of the Whole unit.

Other recommendations include further investment in pathology validation of mouse models and prioritization of projects on rheumatoid arthritis.

- Production results

(cf. http://www.aeres-evaluation.fr/IMG/pdf/Criteres_Identification_Ensgts-Chercheurs.pdf)

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	11
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	0
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	100%
A4: Number of HDR granted during the past 4 years	0
A5: Number of PhD granted during the past 4 years	10

3 • Specific comments

- Appreciation on the results

The overall scientific level of the unit is very good. Several discoveries are highly original and had or may have important clinical applications as proved by the different patent applications. Moreover training of PhD. is also very good with more than 10 students defended their thesis in the past 5 years. The unit has developed stable partnership notably through the establishment/use of different patient cohorts.

- Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners

Performance of the research unit has been very good with respect to scientific publications and patent applications. Multiple patents have been licensed. These research results are expected to positively impact socio-economic partnerships. In addition, the research unit is well capable to fund research activities with external grants. The international recognition is expected to grow if the recent upward momentum is maintained.

- Appreciation on the management and life of the research unit

Management of the research unit with respect to novel science and teaching is in place and performing a good job. There is an excellent atmosphere within the unit, with a noticeable contentment of students and ITA people. This is clearly due to the excellent management and availability of the director. However, the review committee feels that scientific meetings for the whole unit, with attendance of PhD students and staff from both teams, are not structurally planned. To insure cross-fertilization between the two teams, and to better support PhD training, it is recommended to plan such meetings regularly.

All researchers of the unit contribute greatly to teaching with an impressive participation and organization of courses for both medical and biological studies. The unit has also strongly invested in the local structuring of the research with the participation in the scientific committee to clinical research of the hospital, to the administration board of the university but also with the development of a flow cytometry facility open to the whole scientific community.

- Appreciation on the scientific strategy and the project

The overall strategy of the Unit is clearly defined and appears very good. The projects are innovative and use state-of-the-art technology. The investigators have the expertise and the appropriate collaborations needed for their research. The projects are feasible in their hands, although quite demanding.

4 • Appreciation team by team and/or project by project projet

- Title of the team and name of the team or project leader

  Team 1 Immunopathology and biotherapy of muscle diseases

  Olivier BOYER

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		6
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)		1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		3
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)		
N7: Number of staff members with a HDR or a similar grade		5

- Appreciation on the results

  Team 1 worked on 3 major projects: immuno-myology, extracellular nucleotides and regulatory T cells, and functional genomics and pharmacogenomics of rheumatoid arthritis.

  Very good output in terms of scientific publications, such as recent J Exp Med and Faseb J publications, and patents, such as patents for Myoarray and a quantitative assay for SRP antibodies. The number of PhD defences over the past 5 years is very good: indeed, the team has trained 7 PhD students and 11 Master students.

  The muscle-specific models used or under construction in the immuno-myology project are original and have a clear impact on fundamental immunology and myology. The experimental mouse models of myositis so far developed are novel, likely relevant to the human disease, as affected mice develop paralysis reproducing human pathology. The results regarding CD8 T cell tolerance and endopasmic reticulum stress will also open up new avenues for clinical investigations based on these discoveries.

  The rheumatology group has in parallel progressed in the identification of molecular markers of use for diagnostic or drug response prediction. The proteomic analysis of candidate antigens in rheumatoid arthritis are valued by the field of autoimmunity. The effort to identify biomarkers such as gene expression profiles that may predict responsiveness to biologics could have a large impact after further validation in additional groups of patients. Their access and use of large and well-validated patient cohorts is an obvious strength of their studies, allowing the identification and analysis of gene profiles that potentially predict therapy responses in the setting of rheumatoid arthritis.

  The work on the ectonucleotide NAD, its receptor P2X7 and their action on regulatory T cells is well-performed, highly original, and has in all likelihood potential implications.

  In seems that the scientific output of Team 1 has gone upward during the last year or two, which is obviously a very nice and healthy sign. The internal collaboration is stable and synergistic and certainly contributes to

the high quality of the scientific output. The team comprises a very good combination of physician-scientists and basic scientists allowing them to conduct high-ranked translational research.

Collectively, the work from this team contributes original concepts to the fields of autoimmunity and T-cell tolerance.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The leader of the team moved to Rouen on an AVENIR contract in 2005 and has since established a strong team and Unit. The ability of the Team members to raise funds is very good. They have good links with industrial partners, and an excellent ability to network and to establish the appropriate collaborations. It is anticipated that the international visibility of the team will be strengthened thanks to their recently published scientific achievements.

- Appreciation on the scientific strategy and the project

The focus of Team 1 on inflammatory muscle diseases is filling an important niche in France. The strategy and the planned projects are clear, well organized, relevant to human disease and feasible both from a scientific point of view and with regards to human and financial resources. The proposed projects including those improving these existing models are well constructed and feasible. The projects are original and some of them are truly cutting edge.

- Conclusion :
    - Summary

The committee felt this is *very good team* doing translational research on muscle inflammatory diseases. The scientific output is on the rise. Most projects are cutting edge and should lead to original observations.

    - Strengths and opportunities

The translational aspect and the good mix between basic and clinical research.

They occupy a unique niche.

    - Weaknesses and threats

No full-time researcher with permanent position. A potential threat is a tendency to over-interpret the cinical value of established or yet to establish mouse models.

    - Recommendations

Recruitment of a full-time researchers to ensure the positive momentum of the Team is highly recommendable, given the efforts invested and future plans to go from pre-clinical models towards good clinical research and development of novel diagnosis and therapeutic approaches in human diseases.

- Title of the team and name of the team or project leader

  Team 2 Immunopathology and innovative therapy of joint and skin diseases

  Philippe MUSETTE

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)		3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		5
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)		
N7: Number of staff members with a HDR or a similar grade		3

- Appreciation on the results

  Team 2 also worked on 3 projects: skin adverse reactions and T cell responses; role of TLRs in lupus erythematosus; and immune responses in patients treated with biological treatments.

  Team 2 has a very good output in terms of scientific publications and clinical applications. The number of PhD defences over the past 5 years is good. Indeed, the team has trained 4 PhD students and 2 Master students.

  The Team has made major contributions in the field of skin inflammatory disease pathophysiology and treatment over the last 4 years with major publications in top-tier journals such as *N. Engl. J. Med.* and *Science Translational Medicine*. Their novel finding that EBV production is triggered by DRESS-inducing drugs and that virus-specific T cells would be responsible for the very severe auto-inflammatory disease and skin lesions is highly innovative in the field of dermatology and has major clinical implications. Their efforts to sort and analyze B cells and autoantibody production in bullous pemphigoid patients is clearly of importance.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

  The ability of members of Team 2 to raise funds is very good. They have gathered and access to good cohorts of patients both for rheumatoid arthritis (RA) and skin inflammatory diseases. They run the national reference center for autoimmune bullous skin diseases. The principal investigator for the RA projects has good links with industrial partners. Strong national and international collaborations have been developed, most notably with the Singapore immunology network. It is anticipated that the international visibility of the principal investigator will be strengthened thanks to the recently published scientific achievements.

- Appreciation on the scientific strategy and the project

  The committee felt that the projects were of unequal relevance and originality. First, the projects related to the immune-mediated skin diseases (therapy, DRESS,…) are very well-defined, feasible, and highly relevant. Some of them are truly cutting edge. Second, the project investigating the contribution of the IL-10-producing B cell population in immune regulation in human autoimmune diseases is based on preliminary data and

remains speculative. The planned experimental design may not be mature enough to lead to unambiguous answers. And lastly, the projects (based on strong preliminary clinical data) related to identification and validation of biomarkers and the study of their involvement in RA pathophysiology and prediction of responsiveness to given biotherapy (Adalimumab, Ethanercept, etc..) target very important questions and are highly relevant and represent a potential step toward personalized medicine.

- Conclusion :

    - Summary

The committee felt this is a *very good team* performing translational research on skin inflammatory diseases and RA (although formally the latter disease is part of the team's future work).

    - Strengths and opportunities

The translational value of their research and the good mix between basic and clinical research.

The past and present performance meets a high international standard in the field of skin autoimmunity. The scientific output is on the rise. Most projects are cutting edge and should lead to original observations.

They occupy an (inter)national niche with regards to autoimmune skin diseases.

There is an opportunity for further improved international recognition that the project leader should work on, and which should be feasible given his scientific output.

    - Weaknesses and threats

No full-time researcher with permanent position.

Possibly too many projects related to RA (again this relates to the team's future work).

High risk with respect to the IL-10 producing B cells projects.

    - Recommendations

Make all possible attempts to recruit a full-time researcher.

Some caution should be taken about possible dispersion and projects may need to be better prioritized to allow more in-depth investigations. The committee suggests to limit the number of projects and to try to validate the very encouraging results obtained so far on independent cohorts of RA patients.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
PHYSIOPATHOLOGIE ET BIOTHÉRAPIES DES MALADIES INFLAMMATOIRES ET AUTOIMMUNES	**A+**	**A**	**A+**	**A**	**A**
PHYSIOPATHOLOGY AND BIOTHERAPIES OF IMMUNE PATHOLOGIES OF LOCOMOTOR APPARATUS [BOYER-BOYER]	A	A	Non noté	A+	A
PHYSIOPATHOLOGY AND INNOVATIVE THERAPIES OF IMMUNO-DERMATOLOGICAL DISEASES [BOYER-MUSETTE]	A+	A	Non noté	A	A

C1 Qualité scientifique et production
C2 Rayonnement et attractivité, intégration dans l'environnement
C3 Gouvernance et vie du laboratoire
C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	**42**	**5**	**20**	**26**	**36**	**59**	**5**	**17**	**29**	**239**
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

*** les résultats SVE2 ne sont pas définitifs au 06/05/2011.**

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

• SVE1 Biologie, santé
- **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
- **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
- **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
- **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
- **SVE1_LS5 Neurosciences**
- **SVE1_LS6 Immunologie, Infectiologie**
- **SVE1_LS7 Recherche clinique, Santé publique**

• SVE2 Ecologie, environnement
- **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
- **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
- **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

UNIVERSITÉ DE ROUEN

Fait à Mont-Saint-Aignan
Le 15 avril 2011

Le Président

À

Monsieur Pierre Glorieux
Directeur de la section des unités
de recherche
Section 2 – AERES
20, Rue Vivienne
75002 Paris

Réf : S2UR120001262 – Physiopathologie et biothérapies des maladies inflammatoires et autoimmunes (U905) – 0761904G

Monsieur le Directeur,

Je vous prie de bien vouloir trouver ci-joint la réponse formulée par le directeur de l'U905 au rapport d'évaluation de l'AERES.

Je m'associe au directeur de l'Unité pour remercier le comité de visite pour la qualité de son évaluation et celle des échanges.

L'établissement confirme sans réserve son soutient à cette excellente Unité : en plus du recrutement récent d'un MCU-PH et de l'ouverture au concours d'un poste d'IGR, un ingénieur d'études sera engagé à temps complet à partir de la rentrée 2011.

Un autre point à souligner est le financement de l'animalerie avec une enveloppe de l'ordre de 90000€ par an. C'est dire que l'U905 occupe une place centrale dans la politique scientifique de notre Université.

Je vous prie de recevoir, Monsieur le Directeur, l'assurance de ma considération distinguée.

Cafer ÖZKUL

Immunologie, hématologie, pneumologie
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Unité Mixte de Recherche U-905
Physiopathologie et Biothérapies
des Maladies Inflammatoires et Autoimmunes
Pr Olivier BOYER, Directeur

B2012-EV-0761904G-S2UR120001262-RT-BOYER

Pathophysiology and biotherapy of inflammatory and autoimmune diseases

Physiopathologie et biothérapies des maladies inflammatoires et autoimmunes

-

General observations regarding the evaluation report

Observations de portée générale sur le rapport d'évaluation

We thank the visiting committee for its in-depth evaluation of our unit and its valuable comments. We were delighted that the teams have been found '*very good*', and our work to have '*led to highly original results and novel concepts*' with a clinical '*impact beyond doubt*', and that '*the output of the unit is graded as very good*' with regard to publications and patents. The very positive evaluation regarding '*excellent management*', our '*overall strategy … clearly defined*', the '*impressive … organization of courses for both medical and biological studies*' and our '*[strong investment] in the local structuring*' were highly appreciated and very encouraging.

Regarding the recommendations:

- '*Given the quality of science conducted in the Unit, the well-recognized expertise in clinical immunology of the 2 PIs at a national level, the good and well organized collaboration between people, it is anticipated that the Unit should benefit from full time researchers. One way to achieve this goal, and at the same time strengthening the Unit's international visibility and attractiveness to young researchers, would be via the organization of an International course on human Immunology research and/or organizing a conference on Autoimmunity.*'

During the first quadrennial period, we have recruited in Team 1 one post-doc on a permanent position of associate professor (MCU) devoting the major part of his time to research, and recruited a senior MCU with habilitation (HDR) by mobility from another research laboratory. Also, the Director of the unit and the head of Team 2, despite their hospital and teaching duties, spend more than 50% of their time on research. As we indicated in the renewal application, we fully agree with the committee that recruiting full-time scientists on permanent positions is clearly one of our major goal for the next quadrennial/quinquennial period. For this, we will first recruit in the immuno-dermatology group of Team 2 one of our experienced post-doc (currently in Singapore) on a research engineer position that is now officially open for competition in 2011. He will have 100% time devoted to research. We also have another post-doc, already in the unit, that is planned for recruitment in the rheumatology group of Team 2 during the two-year period ahead on the same type of position, with an agreement in principle from Rouen University. In addition to two

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former PhD students currently on a post-doc position (US and Singapore), both teams actively develop their international relations with foreign research centers (Singapore, Hamburg, Buenos Aires and Cordoba notably) so as to facilitate the identification of senior research candidates.

We thank the visiting committee for its suggestion to organize a course/meeting on human immunology/autoimmunity to enhance our national and international visibility. A highly specialized workshop dedicated to immune tolerance and, more particularly, to immuno-myology and muscle autoimmune diseases would indeed help assign to our unit an original position in the field. We are now working on this project. For this, we will take advantage of the scientific relationship that we already have in the field and we will also benefit from the position of the Director of the unit who has recently been elected as Council Member of the International Union of Immunological Societies (IUIS, President S Kaufmann, former Presidents P Doherty and R Zinkernagel). This will favour networking. Also, the Director has been an active member of the organizing committee of a recent international meeting (1st Franco-Argentine Immunology Congress FAIC 2010 in Buenos Aires). We are also in the process of participating to a European network on myositis, and another on AAV muscle gene therapy.

- '*Organize regular joint lab meetings to maintain the scientific discussion and social network between the 2 Teams. In addition, maintain good communication, quality of work and collaboration by a yearly retreat of the whole unit.*'

We are pleased that the committee has found the '*social and scientific atmosphere …very good*'. Indeed, we have structured ourselves so that stimulating work-in-progress meetings are organized on a weekly basis at the level of each team/group and more formal presentations of finalized work are regularly given at the level of the Institute. We have developed many opportunities such as the weekly journal club, the Friday meeting at 12:pm and regular seminars with external speakers that allow members to exchange. Yet, we share the view of the committee that interaction between the 2 teams could be reinforced. We believe that this will be facilitated by our reorganization for the 2012-2015/16 period during which several current members of Team 1 will join Team 2.

In agreement with the committee's recommendation and our discussion during the site visit, we have organized a retreat on March 25th (Cap Hornu, Baie de Somme) where every doctoral student presented his/her work (chairpersons were alternatively the doctoral students themselves) and largely discussed his/her projects with everyone. All unit members concurred to the success of this meeting that was considered by all as a very exciting experience of scientific and social exchange. There is no doubt that we are eager to reiterate this at least on a yearly basis.

- '*Other recommendations include further investment in pathology validation of mouse models and prioritization of projects on rheumatoid arthritis.*'

While mouse models are by definition partly artificial, they remain invaluable tools for investigating disease pathogenesis. We have developed new experimental models such as SM-Ova (expression of a neo-autoantigen specifically in muscle),

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$Rag^{0/0}$ x iMHC (crossing a model of muscle-specific inducible MHC-I expression to an immuno-deficient background) or new transgenic mice conditionally expressing a fusion H-$2K^b$-β2m or H-$2K^b$-β2m-Ovapeptide in muscle. We also use a model of spontaneous myositis in $ICOS^{0/0}$ NOD and $ICOSL^{0/0}$ NOD mice in collaboration with C Boitard (U986). The conjunction of these models will offer unprecedented opportunities to study the different aspects (immunological versus non immunological) of pathogenesis of the different forms of myositis. For higher clinical impact, we use these model in parallel to the analysis of muscle samples from patients that present with the corresponding forms of myositis. This is facilitated by our local recruitment of patients (Internal Medicine department, Dermatology department [for dermatomyositis] and Rheumatology department whose senior members are part of our unit) and by our collaboration with Pitié-Salpêtrière national reference center in Paris and the myology group of Henri Mondor hospital in Créteil. For instance, we have discovered an unexpected role of endoplamic reticulum stress causing severe myopathy in mice and there is now published evidence that a similar phenomenon occurs in selected forms of myositis. Therefore, we are currently studying a series of relevant patients' muscle samples to reinforce the pathological relevance of our experimental work. Also, in a paper recently published in Arthritis and Rheumatism, we have suggested an unexpected pathogenic role of anti-SRP autoantibodies in a severe form of necrotizing myopathy in humans. We are currently investigating this in a mouse model (injection of auto-antibodies from patients) and perform in-depth pathological studies of both mouse and human muscle samples with the clear view that mouse models should be conducted in parallel to human studies.

Regarding prioritization, we have spent significant efforts to focus our projects on a more limited number of objectives than during the first quadrennial period. Team 1 will concentrate only on selected projects in immuno-myology and biotherapy of muscle diseases, and Team 2 on a autoimmune bullous skin disease and mechanisms of drug reaction. The rheumatology group in Team 2 will concentrate on a single inflammatory disease e.g. rheumatoid arthritis with complementary human and mouse studies. Among the numbers of targets that we evidenced from our transcriptomic/proteomic analyses, we have been very selective to choose only two of them for further comprehensive analysis in mice (RasGRP and α-enolase) that correspond to current PhD work. When these PhDs are completed, we will stringently consider the pursuit of these projects depending on the results obtained.

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