LIM - Laboratoire d'immunogénétique moléculaire

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Laboratoire d'immunogénétique moléculaire

From the

Université Toulouse 3

May 2010

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Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

May 2010

Research Unit

Name of the research unit: Laboratoire d'Immunogénétique Moléculaire

Requested label: Equipe d'accueil

N° in the case of renewal: 3034

Name of the director: M. Antoine BLANCHER

Members of the review committee

Committee chairman

Ms. Brigitte AUTRAN, Université Paris 6, Paris

Other committee members

M. Ronald BONTROP, Biomedical Primate Research Centre, Rijswijk, Pays-Bas

M. Jérôme ESTAQUIER, Université Paris 12

Committee members suggested by CNU, CoNRS, CSS INSERM, CSS INRA, INRIA, IRD

M. Antoine TOUBERT, CNU member

Observers

AERES scientific advisor

Ms. Claude-Agnès REYNAUD

University, School and Research Organization representatives

Report

1 • Introduction

- Date and execution of the visit

The lab visit, initially planned on the 6th of January 2010, had to be postponed to the 14th of April, but was perfectly well organized. The visiting committee included four experts with one foreign expert. Presentation included a Director's presentation of his personal carrier and the main Lab scientific accomplishments and projects, then his three collaborators presented their accomplishments and projects, followed by an interview of the collaborators then of the Lab technicians. This presentation was useful to complement some missing points in the written report. The Committee reported its main conclusions to the Director after a closed door meeting at the end of the visit.

The Laboratory was founded in 1987 by the Director and is located in the University buildings of the Faculty of Medicine, close to the Rangueil University-Hospital where all of the Team members are also working (as Hospital-Physicians in the Clinical Immunology laboratory held by the same Director). The Research Team is headed by the current Director and founder of the Lab, and is specialized on the Primate MHC Immunogenetics, a domain in which the Director has a wide international recognition.

- Staff members

The permanent staff is composed of 4 senior scientists with tenure positions, including the Director, 1 Prof (PU-PH) in Immunology retiring in 2011, 2 Assistant-Professors (MCU-PH), together with 1 Senior Lecturer with a strong opportunity for getting rapidly a tenure position (MCU-PH): the 3 latter researchers have performed a solid post-doctoral training in Immunology and molecular Biology, either abroad or in distinct french universities. The staff also includes 1 PhD student and 4 University Technicians, very well trained in Molecular Biology. All researchers collaborate directly with the Director (the PI of all subjects) and between each other but none is PI for any project. The Team is depending upon the Director for all scientific and funding aspects of the research projects, as well as for the students training and technician supervision. The cohesion of the team nevertheless is good.

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4	4
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)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4	4
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	1
N7: Number of staff members with a HDR or a similar grade	2	2

2 • Overall appreciation on the research unit

- Summary :

The Lab's Director has built a university-hospital Team with a solid international recognition on Primate Immunogenetics of the ABO system and MHC complex. The Team discovered three new genes in the ABO family in collaboration with French and Japanese teams, particularly with the discoverer of the ABO gene. The Team developed a solid knowledge on the microsatellites analysis and studied 18 MHC microsatellites in a thousand macaques of various origins. They recently developped novel methodologies to further explore the MHC complex. The Director has developed good connections with Cynomolgus macaque facilities and a strong collaboration with the CEA Macaque platform funded by ANRS. This is the only French Lab on that field.

Another central theme is the immunological study of organ transplantation, in strong collaboration with the Hospital teams. In addition, this small university Lab has developed several other separate research projects including translational researches with the Hospital Lab on immune deficiencies, lymphoproliferative disorders and monoclonal antibody therapy. However the number of publications is moderate (25 over the last five years) in average level to good specialty journals (IF 3 to 6, AIDS, J. Biol Chem., Hum Genetics, Immunogenetics, Tissue Antigens, Am. J. Transplant.).

- Strengths and opportunities

the Director's collaborators to develop their own projects in that field and the ability to supervise students. The Director has built over the last 20 years a series of good works on the Immunogenetics of the ABO system and MHC complex in primates that is unique in France and has acquired a solid reputation in the field. He has established a well-trained team, very good connections with the ANRS-funded cynomolgus platform at CEA, and several durable collaborations with leaders in the field in Japan or in Europe. Overall the team has good opportunities to develop innovative findings in the field of Primate immunogenetics

The Visit Committee recognized the good quality of the work performed and of the existing collaborations, but emphasized the need for a stronger focus on the Lab core subject of Primate Immunogenetics. The Committee also encouraged the Director's collaborators to develop their own projects in that field and their ability to supervise students.

- Weaknesses and threats

Despite the good national or international collaborations, the number of local collaborations appears to be limited. The Director and the team have developed too many side projects far from their core subject, some of them being broad and risky (B-CLL) or depending too much on industrial collaboration (monoclonal therapeutic Antibodies).

The Director has built a team with well trained collaborators participating to each of these programs and strongly collaborating together under the Lab Director supervision, but there is no clear organigram of the researchers involved in each project and none of the collaborators is a PI, nor has developed his/her external collaborations, or applied for specific funds, nor are they entitled to supervise PhD students. As a consequence there are very few students.

A major issue is raised by the regional project of the lab relocalization and dispersion in three distinct sites: Rangueil and Purpan University Hospitals plus the Oncology Hospital while the research lab might either stay in Rangueil or move to Purpan. This project is planned for the end of the next contract period. The committee strongly supports the Director's request to maintain his research and hospital Labs in a single location and recommends to avoid a dislocation and to maintain the proximity of both the University and Hospital labs in a single place either at Rangueil or at Purpan.

- Recommendations to the head of the research unit

The Panel Review committee recommends this small team to focus only on Primate Immunogenetics, a field in which they might become even more innovative, for example by building genome-wide studies, thanks to their good collaborations. The Director's collaborators should develop their own projects in this field and should obtain rapidly authorizations to supervise their own students while maintaining strong internal collaborations.

- Production results : is moderate with 26 over 5 years, 10 published by the Director alone.

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	4
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	ND
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	4/4
A4: Number of HDR granted during the past 4 years	0
A5: Number of PhD granted during the past 4 years	1

3 • Specific comments on the research unit

- Appreciation on the results

The Lab has developed a solid and durable series of novel and seminal findings on the Primate Genetics of the ABO system and MHC complex. This is the only existing French Lab in this field. The relevance and originality of the research is good, as well as the quality and impact of the results in that field. However the number of innovations in the field tends to slower during the last years and the strong collaboration established with ANRS secures the Lab funds but puts this Lab in a service situation more than in a real scientific partnership.

Despite its good recognition, the number and quality of the scientific publications and communications is limited, 26 over the last 5 years, in good but not top-ranked journals . In addition there were only 2 thesis defended.

The overall quality and stability of partnerships is good with collaborations in France, with ANRS, or abroad with Japan, Germany and Spain, but very few collaborations are done locally and the Team is isolated in Toulouse.

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

The number and reputation of the invitations to international conferences and symposia or awards obtained by staff members, including is good for the Director but still very limited for his collaborators.

The Lab director showed his ability to recruit good level senior scientists, but no post-docs and one single PhD student. He did not recruit foreign collaborators or students.

The Lab Director showed a reasonable ability to raise funds, to successfully apply for competitive funding, and is participating to scientific (ANRS) clusters and has set up some industry-funded collaborations but none of his collaborators did so.

The Lab participates to national (ANRS) network on Primate studies and the Director has set up scientific, stable collaborations with foreign partners as mentioned above.

The Lab has produced good scientific findings on the Primate genetics of the ABO glycosyl transferases and MHC class I or class II loci, by focusing on the Mauritius Cynomolgus macaque colonies. The Team has set up very strong links with animal facilities in Mauritius and in France. In addition the Lab has set up two solid collaborations with the industry, one with Novartis on experimental transplant tolerance in macaques (closed) and one with a local biotech on therapeutic monoclonal antibodies.

The Director showed initiatives for scientific animation by organizing an International meeting on Primate Immunogenetics in 2008 during the annual meeting of the European Federation for Immunogenetics (EFI).

- Appreciation on the strategy, management and life of the research unit

The research unit organization appears very pyramidal, and depends only on the Director. The quality of the management is however assessed by the good level of internal collaborations and Lab technicians' spirit, while the communication policy should be strengthened. The research unit staff members have a heavy teaching load that limit their capacity to do research and the structuration of the research team at the local level is concerned by a regional project that will dismantle this relatively fragile structure. Noteworthy the Team shows a modest participation to local researches.

The 3 junior scientists who presented their projects hold permanent positions and have pursued an academic cursus (PhD, post-doctoral training) which should allow them to more actively participate to grant applications as well as students and PhD supervision. The committee strongly encouraged them to defend an "HDR" diploma shortly to fully achieve PI responsabilities.

- Appreciation on the project

  – Existence, relevance and feasibility of a long term scientific project

The main project will focus on the study of factors involved with sensitivity to SIV infection in Mauritius Cynomolgus macaques, in collaboration with ANRS and the CEA Primate facility with which solid links have been built. A large transcriptome analysis is planned comparing human and chimpanzee profiles on the ANRS platform, as well as a study of the repertoire of genes expressed in crab-eating macaques. The influence of the MHC on the severity of SIV infection in the Mauritius colony used by ANRS will be analyzed retrospectively on animals with known characteristics of infection. This project is highly feasible, well funded and should be competitive in the international community given the durable and solid involvement of the ANRS platform in this colony which is becoming central in the global primate resources.

The Director also presented 2 other "risk-taking" projects: 1) on the study of the glycosyl transferases in B-CLL and other lymphoproliferative disorders that constitutes the final element of the Lab research program on the ABO system, but no clear rationale was provided for this study. The study will be conducted with an Hospital team and a lab in Barcelona. 2) A second "risk" project is based on IgA2 monoclonal therapeutic antibodies in collaboration with the Hospital teams. The project will take advantage of a strong collaboration with a local biotech company that develops an IgA2 MAb against CD20 and of the solid training in this field that a junior member of the Team got in in Tours. However this project has no clear scientific rationale or staff organization and is totally dependent on the industry.

  – Existence and relevance of a policy for the allocation of ressources

The Director has secured recurrent fundings from 1) ANRS for projects dealing with the Primate Immunogenetics ananalysis applied to SIV infection and 2) a private company (Cayla) for the monoclonal antibody project. The committee suggested the Lab senior scientists also applied as PI to various funding agencies (ANR or EU…) to broaden the sources of funds.

  – Originality and existence of cutting edge projects

The Lab has acquired a solid reputation and a unique know-how in France on the Primate Immunogenetics. The Committee encouraged the Director and his collaborators to re-focus even more strongly on this theme of excellence.

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

Direction de la Recherche

Toulouse, le 17 juin 2010

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Le Président

au

Président du comité d'experts de l'AERES

Objet : Observations de portée générale sur le rapport d'évaluation
du **"Laboratoire d'Immunogénétique Moléculaire" – EA 3034**
porté par **Antoine BLANCHER**

First of all, the members of the research team are thankful to the members of the scientific committee for their accurate comments and advice. However, some details or precisions are respectfully presented below.

A) The comment : "The Team developed a solid knowledge on the microsatellites analysis and studied 18 MHC microsatellites in a thousand macaques of various origins" has to be actualized. In fact, taking into account the most recent developments of the program, we have studied 24 microsatellites of 1300 animals belonging to four different populations.

B) The comment : "He did not recruit foreign collaborators or students" is not appropriate.

I have organized the stay in my laboratory of Doctor Fumiichiro Yamamoto who has obtained an honorific chair at the Toulouse 3 University (Université Paul Sabatier). During this stay Doctor Yamamoto with his wife Myiako (his research technician) have intensely worked on the characterization of artificial hybrid glycosyltransferase molecules. The results of this study have been published in "Transfusion" (impact factor 2008: 3.475).

Yamamoto F., Yamamoto M., and Antoine Blancher Generation of histo-blood group B transferase by replacing the N-acetyl-D-galactosamine recognition domain of human A transferase with the galactose-recognition domain of evolutionarily related murine a1,3-galactosyltransferase TRANSFUSION Volume 50, March 2010 pages 622-630.

In collaboration with Dr. F. Yamamoto, I have written an article of general review on the ABO gene molecular biology. This article corresponds to a chapter of a book on blood groups which will be published at the end on 2010. Before and during the stay of Dr. Yamamoto, I have written and conducted the project on the study of glycosyl-transferases in chronic B leukemia. Despite Dr. Yamamoto has moved in Barcelona (he is now Senior Group Leader in the IMPPC, Institut de Medicina Predictiva i Personalitzada del Càncer), our collaboration is continuing in the latter field.

.../...

C) The comment «the number of local collaborations appears to be limited» does not reflect the actual situation.

1) We have collaborated with the research team of Louis Casteilla (CNRS) and the team of Philippe Bourin (EFS) of the IFR150. With them we have characterized the immunosuppressive properties of the adipose mesenchymal stem cells and compared their properties with those of bone marrow mesenchymal stem cells and of fibroblasts. The results of our collaborative studies have been published in 2005 and 2010.

Puissant B, Barreau C, Bourin P, Clavel C, Corre J, Bousquet C, Taureau C, Cousin B, Abbal M, Laharrague P, Penicaud L, Casteilla L, Blancher A. Immunomodulatory effect of human adipose tissue-derived adult stem cells: comparison with bone marrow mesenchymal stem cells. Br J Haematol. 2005 Apr;129(1):118-29.

Cappellesso-Fleury S, Puissant-Lubrano B, Apoil PA, Titeux M, Winterton P, Casteilla L, Bourin P, Blancher A. Human Fibroblasts Share Immunosuppressive Properties with Bone Marrow Mesenchymal Stem Cells. J Clin Immunol. 2010 Apr 20. [Epub ahead of print]

2) We have intensely collaborated with mister Jean-José Maoret, the engineer of the molecular biology platform of the IFR150. More recently we have collaborated with the engineers of the Genotoul platform to initiate the 454 high throughput sequencing program.

3) we have collaborated with several clinical teams of our hospital particularly with the team of Pr. Lionel Rostaing and Pr. Nassim Kamar of the transplantation department.

Puissant-Lubrano B, Rostaing L, Kamar N, Abbal M, Fort M, Blancher A. Impact of rituximab therapy on response to tetanus toxoid vaccination in kidney-transplant patients. Exp Clin Transplant. 2010 Mar;8(1):19-28.

Kamar N, Milioto O, Puissant-Lubrano B, Esposito L, Pierre MC, Mohamed AO, Lavayssière L, Cointault O, Ribes D, Cardeau I, Nogier MB, Durand D, Abbal M, Blancher A, Rostaing L. Incidence and predictive factors for infectious disease after rituximab therapy in kidney-transplant patients. Am J Transplant. 2010 Jan;10(1):89-98

D) Number of publications:
Recently the members of the research team have published the following articles. I would like to know if they the committee has the possibility to take them into account.

Cappellesso-Fleury S, Puissant-Lubrano B, Apoil PA, Titeux M, Winterton P, Casteilla L, Bourin P, Blancher A. Human Fibroblasts Share Immunosuppressive Properties with Bone Marrow Mesenchymal Stem Cells. J Clin Immunol. 2010 Apr 20. [Epub ahead of print]

Puissant-Lubrano B, Rostaing L, Kamar N, Abbal M, Fort M, Blancher A. Impact of rituximab therapy on response to tetanus toxoid vaccination in kidney-transplant patients. Exp Clin Transplant. 2010 Mar;8(1):19-28.

Aarnink A, Estrade L, Apoil PA, Kita YF, Saitou N, Shiina T, Blancher A. Study of cynomolgus monkey (Macaca fascicularis) DRA polymorphism in four populations.
Immunogenetics. 2010 Mar;62(3):123-36. Epub 2010 Jan 22.

Yamamoto F, Yamamoto M, Blancher A. Generation of histo-blood group B transferase by replacing the N-acetyl-d-galactosamine recognition domain of human A transferase with the galactose-recognition domain of evolutionarily related murine alpha1,3-galactosyltransferase. Transfusion. 2009 Nov 20. [Epub ahead of print]

Collaborative publications:

Iriart X, Witkowski B, Courtais C, Abbes S, Tkaczuk J, Courtade M, Cassaing S, Fillaux J, Blancher A, Magnaval JF, Pipy B, Berry A. Cellular and cytokine changes in the alveolar environment among immunocompromised patients during *Pneumocystis jirovecii* infection. Med Mycol. 2010 May 17. [Epub ahead of print]

Kamar N, Milioto O, Puissant-Lubrano B, Esposito L, Pierre MC, Mohamed AO, Lavayssière L, Cointault O, Ribes D, Cardeau I, Nogier MB, Durand D, Abbal M, Blancher A, Rostaing L. Incidence and predictive factors for infectious disease after rituximab therapy in kidney-transplant patients. Am J Transplant. 2010 Jan;10(1):89-98

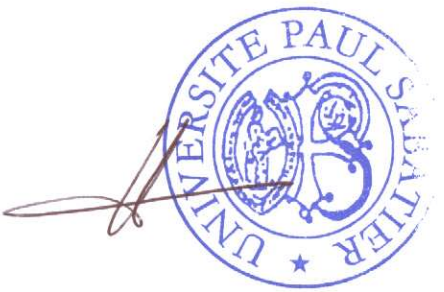
Kita YF, Hosomichi K, Kohara S, Itoh Y, Ogasawara K, Tsuchiya H, Torii R, Inoko H, Blancher A, Kulski JK, Shiina T. MHC class I A loci polymorphism and diversity in three Southeast Asian populations of cynomolgus macaque. Immunogenetics. 2009 Sep;61(9):635-48. Epub 2009 Aug 1.

.../...

E) Focusing of the thematics.

The research team tried to focus his research programs around his competence in the immunogenetics of nonhuman primate. However, it was not possible to discontinue immediately old themes which remain productive such as the study of the ABO glycosyltransferases and related genes. Other themes, such as the study of recombinant monoclonal antibodies, have been proposed with the intention to valorise the expertise of the laboratory in the manipulation of the nonhuman primate model. In this context, the study of Fc receptors nonhuman primates will be develop through a collaboration with Pr Hervé Watier and his reseach team.

All members of the laboratory are convinced that a better scientific production could be obtained by a stronger focus on the core subject of primate immunogenetics. However, this is possible only if the nonhuman primate immunogenetics expertise is applied to various fields such as immuno-virology in collaboration with Roger Le Grand, monoclonal antibodies and Fc receptors in collaboration with Hervé Watier. In this context the Director's collaborators will have the possibility to supervise students and develop their own projects. The laboratory has the ambition to not only develop his expertise of the nonhuman primate immunogenetics but also to validate its findings in human. As it was mentioned during the visit of the scientific committee, the final aim of the research team is to improve the comprehension of human immuno-pathology and immunotherapy through the appropriate use of the nonhuman primate models by taking into account the genetic diversity of the animals.



Gilles FOURTANIER