Immunobiologie des infections a trypanosoma

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Immunobiology of Trypanosoma infections

From the

Pasteur Institute

Mai 2010

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Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

Mai 2010

Research Unit

Name of the research unit: Immunobiology of Trypanosoma infections

Requested label: Pasteur unit

N° in the case of renewal

Name of the director: Ms. Paola MINOPRIO

Members of the review committee

Chairperson:

Mr. Adrian HAYDAY, London, UK

Other committee members

Mr. Robert SCHREIBER, Saint Louis, USA

Mr. Lewis LANIER, San Francisco, USA

Mr. Ricardo GAZZINELLI, Belo Horizonte, Brazil

Mr. Hans-Reiner RODEWALD, Ulm, Germany

Mr. Georgio TRINCHERI, Frederick, USA

Mr. David LEVY, New-York, USA

Mr. Michel NUSSENZWEIG, New-York, USA

Mr. Per BRANDTZAEG, Oslo, Norway

Mr. Bruno LUCAS, Paris,

Ms. Danila VALMORI, Nantes

Observers

AERES scientific advisor

Ms. Claude-Agnès REYANUD

Report

1 • Introduction

- Date and execution of the visit

This visit, which took place on the 30th of November and the 1rst of December 2009, represents the first attempt, for AERES and Pasteur Institute, to merge their own evaluation procedures in order to avoid unnecessary duplication of site visits. In this still provisional setting, each Pasteur group was evaluated independently, without consideration for their being embedded within a larger INSERM or CNRS structure. Accordingly, a general report commenting on the activity of the Immunology Department is provided, but not on the INSERM or CNRS unit entities.

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
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)	2	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	3
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	1	1

2 • Overall appreciation on the research unit

- Data on the work produced :

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	2
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	0
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	2/2
A4: Number of HDR granted during the past 4 years	0
A5: Number of PhD granted during the past 4 years	2

3 • Specific comments on the research unit

- Appreciation on the results

Initial studies performed by the group leader described a polyclonal activation of lymphocytes as a central event in the pathogenesis of Chagas' disease. More precisely, by eliciting a polyclonal activation of lymphocytes, induction of parasite-specific immune responses is avoided, thus favoring evasion of host effector mechanisms. Furthermore, by activating self-reactive clones, polyclonal activation would contribute to the development of an « autoimmune » process, responsible for myocarditis during Chagas disease. The current research of the group is focused on the discovery of the Trypanosoma cruzi proline racemase (PRAC), the first PRAC reported to be in eukaryotic cells. In this study, PRAC was also described to be a potent B cell mitogen, and suggested to have a central role on polyclonal B cell activation elicited during acute infection with T. cruzi. During the last five years, studies of this group were oriented toward the biochemical characterization of PRAC structure and function. Crystals were generated, leading to the characterization of its tridimensional structure. In addition, a biochemical method was established to measure PRAC activity, allowing the screen of a large number of small compounds, as inhibitors of PRAC activity. These represent a very logical set of studies in contemporary molecular parasitology, that aims to understand PRAC function, and its potential utility as drug target for chemotherapy of Chagas disease.

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

The head of the group is an internationally recognized leader in the field of immunology of T. cruzi. In the last ten years she is perceived as having somewhat switched direction in order to focus on the protein structure and enzymatic activity of PRAC. Nonetheless, this is with the goal of treating a serious parasitic disease. The quality of her work is well-recognized by leaders in the field of molecular parasitology.

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

The major project of the group is very well focused and has made progress during the four past years. The collaborative studies with the Brazilian group at Oswaldo Cruz Foundation and the Structural Biology/Bioinformatic groups at Institut Pasteur have been rewarded with a positive outcome, and these collaborations might usefully be maintained. However, it is undeniable that the productivity of the group in terms of scientific papers has been very modest, and there has likewise been limited ability to raise funds from external sources. It is recommended that much more attention be paid to these basic aspects of lab management. The laboratory is small and currently has

three technicians/engineers and one PhD student. One researcher was recently recruited to the group. During the evaluated period, the laboratory had one post-doctoral fellow for three months, and one for 33 months; as well as two visting scientists for a period of two months each. In addition, the group leader supervised one PhD student and one Masters Student from University Pierre and Marie Currie, and co-supervised one PhD student from Federal University of Rio de Janeiro, Brazil.

- Appreciation on the project

For the next four years, this research group intends to continue evaluating the effectiveness of PRAC inhibitors as potential trypanosomicidal drugs. In addition, it is planned to evaluate the role of this enzyme on both T. cruzi and T. vivax, the only other trypanosomatide found to contain PRAC genes. Finally, the group intends to define the mechanism by which PRAC activates B cells and other cells from the immune system, and the possible involvement of Toll-like receptors. All these goals are relevant and feasible in four years. Considering the suitability of this laboratory being set within the Department of Immunology, one would hope to see benefits that strengthen her research on immunological aspects of PRAC as well as on T. cruzi/T. vivax infections. However, the original studies of polyclonal lymphocyte activation that opened up interesting possibilities in immunology are not now a focus. Instead it is inescapably true that the research thrust is first and foremost on the parasite. It is therefore difficult to argue against the logic of re-locating this laboratory to the Dept of Parasitology, complementing that Dept's research, and relieving an opportunity-cost for the Dept of Immunology. The generation of transgenic or knockout T. cruzi parasites is performed in several labs in the world in a routine basis. While a molecular biologist was recently recruited to the group, for establishing the techniques to engineer parasite knockouts for PRAC gene, the group may benefit from collaborating with a research group that routinely generates transgenic/knockout T. cruzi parasites.

- Recommendations

The committee would advise that the research be continued in a small-scale, highly focused initiative, primarily affiliated with the Parasitology department.

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	B	A	A	A

INSTITUT PASTEUR

Laboratoire d'Immunobiologie des Infections à Trypanosoma

Paris, le 14 Avril 2010

A l'Attention de la Direction de la Section Recherche, AERES and Members of the Site Visiting Committee

Objet : Laboratory Immunobiology of Trypanosoma Infections, Evaluation-December 2009

Dear Sirs/Mesdames,

First I would like to take this opportunity to thank the members of the AERES and Site Visit Evaluation Committees for conducting a pleasant and efficient evaluation. We appreciate very much the Committee's useful suggestions concerning specific aspects of our research and its future development, most of which correspond to plans already elaborated.

Nevertheless, we had hoped that the Committee might have noted two other aspects of the laboratory's work: (i) our strong implication in valorisation activities as evidenced by our patent portfolio, and (ii) several publications *in press*, under revision or submitted.

Finally, we thank the Committee for its endorsement of our goals and its encouragements regarding future laboratory activities in a context of long-term sustainability. This will certainly lend an enhanced legitimacy to the group, providing additionally a positive benefit to PhD students and post-docs. It should also promote participation of the laboratory in external projects including intra-Pasteur research networks and European and other international research organizations, paving the way for additional multidisciplinary initiatives.

Sincerely yours,

Paola MINOPRIO
Head of the Laboratory

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