

Cytokines et développement lymphoïde

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Physiopathologie du système immunitaire

From the

INSERM

Pasteur Institute

Mai 2010



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et de l'enseignement supérieur

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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: Physiopathologie du système immunitaire

Requested label: UMR_S INSERM

N° in the case of renewal: U668

Name of the director: Mr. James DI SANTO

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

Committee members nominated by staff evaluation committees (CNU, CoNRS, INSERM and INRA CSS....)

Ms. Danila VALMORI, Nantes, for the INSERM CSS5

Observers

AERES scientific advisor

Ms. Claude-Agnès REYNAUD

Research Organization representatives

Ms. Christine TUFFEREAU and Armelle REGNAULT, INSERM



Report

1 • Introduction

- Date and execution of the visit

This visit, which took place on the 30th of November and the 1st 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)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	15	13
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	11	10
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)	8	8
N7: Number of staff members with a HDR or a similar grade	6	6



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	10
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 $[(A1)/(N1 + N2)]$	10/10
A4: Number of HDR granted during the past 4 years	0
A5: Number of PhD granted during the past 4 years	9

3 • Appreciation team by team

Title of the team: Cytokines et développement lymphoïde

Name of the team or project leader: James Di Santo

- 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)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	7	7
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4	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)	2	2
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

Since the last review, the group leader and his team have made seminal contributions to the understanding of the differentiation and development of Natural Killer cells, have identified a novel immune cell type in the gut that is characterized by secretion of IL-22, and have devised a newly improved mouse model supporting the development of



a human immune system. Their accomplishments are well documented by publication in top-tier journals including the JEM, Immunity, and Nature Immunology.

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

The group leader is an internationally recognized expert in the field of cytokine biology and Nature Killer cell differentiation. He is frequently asked to participate in international conferences and workshops in this area, and of note was asked to write the definitive review of NK cell differentiation for the Annual Review of Immunology, the most highly cited scientific review journal.

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

The group leader has an outstanding research team staffed by highly talented and motivated scientist, fellows, and students. In addition, it should be noted that he is PI of one of the highly competitive Gates Grand Challenge grants and successfully coordinates an international team of investigators to achieve the goals of this program.

- Appreciation on the project

The group has outlined an ambitious and outstanding research plan with two major goals. First, this team will continue their innovative and groundbreaking studies of the transcriptional factors controlling the development of NK cells. The proposed studies are feasible, logically designed, and promise to provide important new insights into this area. The other major initiative in the Unit is to optimize the development of a human immune system in immunocompromised mice, a program supported by the Gates Foundation. This is a high-risk, high-reward project that is very technically demanding and requiring considerable financial resources. The goals of this project are very important to the scientific community; however, the review committee recommends that this project not detract from the group leader's efforts toward other programs in the unit.

Title of the team: Développement des lymphocytes

Name of the team or project leader: Ana Cumano

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	4	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	5
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	4
N7: Number of staff members with a HDR or a similar grade	4	4



- **Appreciation on the results**

The group has made major contributions to the study of haematopoietic stem cell development. Their research strategy is unusual and in some areas unique, with genuinely exciting data emanating from very challenging studies that seek to identify the earliest embryonic foundations of haematopoietic potential. Their compelling visualization of juxta-endothelial progenitors that precede fetal liver colonization is particularly noteworthy, and a foundation for future original studies that have genuine potential to become text-book data. These experimental accomplishments have led the group leader into some high profile and effective collaborations, either with other Pasteur departments or outside the Institute.

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

The group leader is an internationally recognized pioneer and leader in haematopoietic cell development, reflecting which she is the author of a relatively recent review of her area in *Annual Review of Immunology*, the most prestigious and highly-cited review journal of the field. One member of this group -who is also an active teacher- is relatively young as an independent investigator, but her focus on splenic haematopoiesis is creative and unusual and likely to earn her an international reputation with time. Other members of the team with independent research programmes are well known, and their work is considered thoughtful, reliable, and creative. One of them has been involved in some highly incisive external collaborations, particularly those with a world-leader group in gamma delta cell specificity at Stanford. However, one inescapable observation is that the primary drivers of the major high-impact publications are often the external collaborators.

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

The composition of this team is unusual. Rather than building a critical mass focused on the own specific area of the group leader and on closely juxtaposed ones, the research team covers a broad spectrum of project areas spanning regulatory T cells; B cell development; gamma delta T cell development and specificity; and splenic haematopoiesis, respectively. Pursuing these different projects in this type of organization poses obvious challenges. Perhaps the two most fundamental are the establishment of individual critical mass in each area, and the capacity to develop incisive, cross-group cohesion. The lack of obvious cohesion suggests that the results of the Unit might never exceed the sum of its components parts. Overall, the Unit lacks a clearly articulated strategy that addresses these issues.

- **Appreciation on the project**

The group leader's project trajectory is excellent. She is clearly adopting molecular approaches, which is a necessary albeit an ambitious plan given the rarity of the cells under study. But, she has the necessary cellular skills, and the committee expectation is that colleagues within and beyond the department should be able to provide key molecular advice. Hence, the expectation can be for cutting-edge output. The other research plans were underpinned by consistently creative and original thinking, and in each area, there are major unresolved questions that can be usefully addressed. However, it might be argued that more attention might be devoted to the practical aspects of project development; timelines; milestones; and competitiveness. These issues are exacerbated by the lack of critical mass in some highly competitive areas, and by the lack of clear cross-area cohesion: it is not always obvious that the studies being pursued benefit from being in group leader's Unit, or that the group leader's Unit particularly benefits from the pursuit of the proposed studies. The most obvious exception to this would be the work on splenic haematopoiesis, which does more closely relate to the group leader's focus.

- **Conclusions**

Overall, there is research of high quality in this grouping and this should be maintained in the interests of scholarship and of its significance to Institut Pasteur. However, for several research leads of the group, the regularity, volume and impact of research publications make it challenging to maintain competitiveness at the highest international level.



Title of the team: Dynamics of immune responses

Name of the team or project leader: Philippe Bousso

- 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)	1	1
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)	2	2
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)	2	2
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

This group has made an excellent start to his independent career through the G5 mechanism. This no doubt reflects the exceptional talent of the team leader and the very supportive environment that he has been provided. His application of two photon microscopy to image in vivo is not unique but he has been in the vanguard of this research since his very productive post-doctoral period in at Berkeley, and his application of it continues to be convincing in technical terms, and compelling in biological terms. His documentation of clear differences between NK and T cell dynamics are extremely provocative and hypothesis-generating. Likewise, his studies on immune interactions with tumours in situ are important and incisive, albeit that the tumour model systems are currently very basic. Not surprisingly, these studies have earned him a fine publication portfolio of important papers in reputable journals. They have also laid a foundation for some exciting collaborations with members of the Dept., and others outside it.

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

The group leader is already an internationally recognized pioneer and leader in his field. At a relatively young age, he was invited to deliver a plenary lecture at the International Immunology Congress in Rio (2007), and the reviews solicited concerning his requested transition from G5 to Unit status reveal a uniformity of respect for him among his peers.

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

The group leader has constructed a small, highly international research team. Based on the quality of the written documentation provided; on the excellence of his oral presentation; and on meeting the team in his absence, the committee would judge the laboratory to be extremely well-managed, with a very clear research strategy. Even the limited physical space of the laboratory appears very well organized. This clearly lays a strong foundation for the proposed expansion of personnel and space for this group.

- Appreciation on the project

The group very clearly outlines discrete project areas for further development. The strategy is logical and is good, because the projects have intrinsic worth and because they benefit from likely synergies. The only concern, strongly felt by the review board, is that the group could be encouraged via a combination of collaboration and junior faculty mentorship to respond more creatively to some of the very interesting hypotheses that their work generates. To cite two examples: there was no clear path to identifying how NK cells are apparently able to integrate



information more rapidly than cytolytic T cells; and the choice of infectious disease system to study by 2-photon imaging might have benefited from a genetically tractable one where the effects of determinants of virulence might be directly visualized for the first time - the renowned expertise in microbiology at the Pasteur would seem an ideal platform for such investigations. These concerns are not to diminish enthusiasm for the proposed programme. Rather, they reflect a conviction that the group leader is well-placed to devote some part of his portfolio to ground-breaking and ambitious collaborative projects that will generate exciting new knowledge, and continue to enhance his and the Institut Pasteur's reputation.

- Conclusion

The Committee recommends that the group be allowed to expand as soon as possible. Overall, this group should serve as a role model to other G5 investigators, and the Institut's response to its success should define its capacity to reward success.

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



Nom de l'équipe : DYNAMIQUE DES RÉPONSES IMMUNES

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+

Nom de l'équipe : DÉVELOPPEMENT DES LYMPHOCYTES

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+	B	A

Nom de l'équipe : CYTOKINES ET DÉVELOPPEMENT LYMPHOÏDE

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+

Rebuttal for AERES report EVAL-0755366A-S2110044615

Inserm U668, Institut Pasteur

Director: James Di SANTO

Date of Evaluation: December 2009

The Inserm U668 includes three Pasteur research structures (headed by James Di Santo, Ana Cumano and Philippe Bousso) that pursue a diverse set of complementary scientific projects in fundamental and applied immunology. Many of the Unit's collaborative studies have led to publications with co-authorships, attesting to the effective cohesion within the Unit as a whole and within the individual laboratories that make up the U668. This point was clearly appreciated by the AERES committee that evaluated the U668 in April 2008 (ranking: A+; see <http://www.aeres-evaluation.fr>).

While the AERES committee that evaluated these same three Pasteur laboratories in December 2009 gave similar praise for the overall scientific accomplishments of the researchers within the U668, we were disappointed that the site-visit committee was unable to remain objective in assessing the work on gamma-delta T cells performed within one of the laboratories. This work, while collaborative, involved shared participations and equal contributions. We strongly disagree with the committee's conclusion that the publications in question were driven primarily by the efforts of the external collaborators. Furthermore, we would like to point out that, since this particular project is not included in the overall scientific program of the U668, these critiques are irrelevant to the U668 evaluation.

14 April 2010



JAMES P. DI SANTO

James Di SANTO

Director, Inserm U668

A handwritten signature in black ink, appearing to read 'A. Israël', with a large, sweeping flourish extending downwards and to the right.

ALAIN ISRAËL
DIRECTEUR DE L'EVALUATION
SCIENTIFIQUE
INSTITUT PASTEUR