ARHSI - Activation, relaxation et homéostase du système immunitaire

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Activation, relaxation and homeostasis of the immune system

From the

CNRS

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: Activation, relaxation and homeostasis of the immune system

Requested label: URA CNRS

N° in the case of renewal: 1961

Name of the director: Mr. Antonio FREITAS

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

Ms. Danila Valmori, Nantes

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

Mr. Bruno Lucas, Paris

Observers

AERES scientific advisor

Ms. Claude-Agnès Reynaud

Research Organization representatives

Ms. Evelyne Jouvin-Marche, CNRS

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

This table includes the group of S. Longacre, and of F. Lemonnier for past members only. The group of S. Longacre was evaluated with the Parasitology department.

	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)	4	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	23	17
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	13	12
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)	13	10
N7: Number of staff members with a HDR or a similar grade	15	13

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	4
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	16/18
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	4
A4: Number of HDR granted during the past 4 years	1
A5: Number of PhD granted during the past 4 years	14

3 • Appreciation team by team

Title of the team: Biologie des populations lymphocytaires

Name of the team or project leader: Antonio Freitas

- 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)	5	5
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)	3	3
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

Generation, maintenance and decay of lymphocyte populations follow tightly regulated processes. Once deranged, imbalances in this flow can be associated with defects ranging from lymphoproliferative to immunodeficiency syndromes. This remains therefore an important, and perhaps understudied area in immunology. The group leader has a long-standing interest in the quantitative and qualitative analyses of the basis of lymphocytes homeostasis in vivo. His contributions to this field are very original, if not unique, and his laboratory has been very productive. While in vivo lymphocyte lifespans were initially analyzed by cell transfer experiments and proliferation-labeling studies in normal mice, the group has more recently made significant progress in elucidating important regulatory mechanisms involving molecular factors such as Fc receptors and immunoglobulin levels for B cells, and cytokines and cytokine signaling pathways for T cells. This work has revealed new and significant data on lymphocyte selection and competition for space (niches) and resources such as access to growth factors.

- 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 leading and highly recognized expert in the field of lymphocyte homeostasis. Independent and original approaches are used to tackle these complex questions by in vivo analyses and met with widespread and sustained interest. This work is published in very good peer-reviewed journals, and includes highly cited papers. The standing and visibility of the team is evident from the fact that the group leader is frequently asked to comment on new developments in the field in News and Views types of articles, and he is an author of influential reviews. He has a novel "tractus" on immunology in press. Moreover, his work was received positively in the recent, highly competitive ERC grant application round.

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

The immediate laboratory of the group leader has highly motivated, young students and postdocs who are driven to conduct original, conclusive and relevant projects. They are well on their way to generating the tools including complex mouse crosses required to address the future aims of the laboratory.

The reviewers had, on the other hand, the impression that the Unit was somewhat less coherent on its overall research structure. In particular, the work of one scientist of the group on the development of mice as suitable recipients for human hematopoietic stem cells, and the work on human ES cell differentiation into hematopoietic stem cells both represent new and additional thrusts for the Unit. These projects are certainly original and worthwhile in their own right. The committee notes, however, that similar work is ongoing in another laboratory of the same department, with no obvious co-ordination of the two approaches. Since it frankly cannot be predicted which approach is eventually going to be successful in this important and highly competitive area, the Scientific Review Committee suggested that this research be continued. It felt, however, that it might be useful for this research effort to be re-organized, into one that is more consolidated within the Department.

- Appreciation on the project

The group has a very interesting and ambitious research plan. In the future, a major focus of the laboratory will be on the homeostasis of regulatory T cells (Treg). Very stimulating preliminary data were presented to suggest that Treg are under different, and as yet poorly understood control mechanisms as opposed to 'conventional' T cell populations. In the B cell area, the research plan is to extend the work from naïve lymphocyte populations to the turnover and maintenance of memory B cells and B cells with autoimmune specificities. The planned analyses of the homeostasis of post-antigen reactive B cells will require yet another level of complexity of experimentation but the review committee had no doubt that the group leader will master these projects. Novel insights into the life span, and its regulation, of Treg and antigen-experienced B cells shall be relevant for many aspects of basic and applied immunology.

Title of the team: Signalisation des cytokines

Name of the team or project leader: Sandra Pellegrini

- 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)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	3
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)	3	2
N7: Number of staff members with a HDR or a similar grade	3	3

- Appreciation on the results

The unit focuses mainly on the regulation of the IFN pathway, an outgrowth of pioneering work that identified Tyk2 as the first tyrosine kinase implicated in IFN signaling and that uncovered differential receptor utilization by the family of IFN isotypes, leading to a series of studies on IFNa/b differentials. More recently, the group has expanded its interest into signaling in CD4 T cells, including studies on TCR signaling as well as on the impact of IFN, largely through the efforts of a senior scientist within the group. The work accomplished in the past 4 years represents solid contributions to the understanding of the biochemistry of signaling and demonstrates a highly collaborative effort with other scientists in France and elsewhere. Many of the studies involved a highly reductionist approach, using well-defined cell lines expressing or lacking individual signaling molecules. A few of the findings were also extended to primary cell contexts, particularly through the use of primary human T lymphocytes. The studies resulted in a total of 21 primary and collaborative publications, largely in mid-tier journals appropriate to the field, and with some higher-impact publications, such as in J. Exp. Med., PNAS, Blood, and MCB. Overall, a somewhat greater level of productivity might be expected for a group of this size in the supportive environment of the Pasteur Institut, perhaps due to limited funding from external sources. Improvement in this area should be a priority in order to avoid a negative impact on future research prospects.

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

The team is well known in the field and its leader has become recognized as an expert on Tyk2 structure and function. With the realization that this enzyme may be implicated in a number of human diseases, her expertise has become an even more important resource.

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

Although the written report sent to the committee may not have done full justice to the science, the team leader gave an excellent presentation to the committee, demonstrating a firm grasp of the science and its future directions. Of particular note was the performance of her students, one in particular giving an excellent presentation, demonstrating the team leader's firm commitment and skill in teaching. Of possible concern was the integration of her work with that of one senior scientist who works mainly on negative regulation of TCR signaling. However, there are clear signs of increasing interaction and synergy in this area, with this scientist looking at IFN-TCR signaling and the team leader expanding into primary T cell studies.

- Appreciation on the project

A series of 5 projects is proposed for the next four years in the written report, and has both strengths and weaknesses.

1. IFNa2/b differential and translational control. This project is based on the observation that IFNa2 and IFNb exhibit equally potent inductions of Jak-Stat signaling and gene expression and yet differ markedly in the induction of apoptosis. A series of siRNA silencing experiments are proposed to test the role of possible signaling proteins in this process, and how the individual receptor components transmit this differential activity will be examined. How individual regions and/or residues in the IFNAR chains will be defined as participating in differential responses is not made clear and may prove difficult. Studies are also proposed to investigate the intracellular trafficking of IFN-receptor complexes. A potentially fruitful approach will involve a proteomic approach, in which biotinylated IFN will be used to retrieve protein-protein complexes for identification by mass spectroscopy. This is an open-ended approach that could yield interesting and novel results.

2. Differential desensitization to IFNa and IFNb. Another aspect of differential functions of IFNa and IFNb is their distinct responses in cells previously desensitized to type I IFN. A number of biochemical experiments will be conducted to determine if ISG15 conjugation is involved in this response, an area of current interest in the field. The practical outcome of these studies, which could be important for HCV therapy, is uncertain, but they represent an intriguing direction with some exciting preliminary data.

3. Functional analyses of Tyk2 variants of potential impact on pathogenesis. GWAS have implicated Tyk2 variants in a number of human diseases, including autoimmune syndromes and cancer, but no mechanistic understanding of this association has been provided. In a continuation of studies on the potential role of activating mutations in Tyk2 in disease, a number of cell line-based experiments are proposed to explore biochemical and signaling differences among several naturally occurring Tyk2 variants. These experiments could prove to provide very interesting results, although the number of patient samples with defined Tyk2 alterations is unclear. Analysis of the results may also be complicated by the possibility of bystander effects due to the underlying autoimmune syndrome. Coupling this approach with, for instance, a knock-in mouse model of Tyk2 variants might prove helpful, if available. Overall, biochemical characterization of naturally occurring Tyk2 variants associated with disease was considered a valuable and essential approach that will provide important information for the field.

4. Influence of type I IFN on CD4+ T cell activation and function. A series of experiments are proposed to explore crosstalk between TCR and IFN signaling, particularly with regard to IL-10 production. Presumably the goal of these studies is to examine the hypothesis that altered T cell regulation by IFN may underlie diseases associated with Tyk2 variants. The demonstrated ability to work effectively with primary T cells is a significant strength of these proposed studies.

5. Negative regulation of T cell activation through the transmembrane adaptor LAT. Continuation of studies of the role of LAT, Dok-1, and Dok-2 as negative regulators of TCR signaling is proposed. The underlying hypothesis of these studies is that the strength of TCR signaling can be modulated in a complex fashion and may impact on the development of autoimmunity.

- Recommendations

The Committee felt that this is a productive unit with a solid future in elucidating mechanistic details of innate immunity. It was felt that the unit occupies an important research niche, particularly with its attention to the differential activities of distinct Type I IFNs, the role of Type III IFN in innate immune responses, and the potential role of Tyk2 mutations in human disease. However, more effort should be devoted to focusing and integrating the efforts of the unit, and a greater utilization of the strengths of the Pasteur Institut in infectious diseases could be of significant benefit.

Title of the team: Biologie cellulaire des lymphocytes

Name of the team or project leader: Andrès Alcover

- 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)	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)	5	5
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	3	3

- Appreciation on the results

This group has been highly productive over the past 4 years, publishing a number of high-impact papers that described highly significant and in some cases paradigm-shifting results, particularly his discovery of biofilms in virus spread. It has built expertise in multiphoton and time-lapse microscopy; is exploring the capabilities of the Amnis ImageStream platform for quantitative cell biological measurements; and has applied imaging technology effectively to studies of the T cell synapse. The group has made important strides in defining the connection between the immunologic synapse and the T cell cytoskeleton and in defining mechanisms regulating the movement and heterogeneity of signaling assemblies. Also of importance has been their attention to lymphotropic retrovirus infections, particularly HTLV-1, a somewhat understudied virus.

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

The work is interdisciplinary and diverse, impacting a number of distinct fields. It has resulted in 11 publications in the past 4 years, plus 2 manuscripts in the process of submission, including 1 now accepted for publication in Nature Medicine. Publications included high-impact general interest journals, such as Immunity, EMBO J, and J. Exp. Med., as well as appropriate specialized journals, such as PLoS ONE, and J. Immunol., and several high profile reviews, demonstrating high caliber work and visibility. Citation frequency of the individual articles is high, which along with the invitations for review articles is strong evidence of significant international esteem. The group is well funded from internal and external sources and has established important collaborations, both within Pasteur and outside.

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

The group's activities provide a classic approach to cell biology and virology: using viruses to probe normal mechanisms of cell biology and using the information obtained to better understand viral pathogenesis. Their combination of biochemical, genetic, and imaging techniques provides a coherent and broad-based approach to important problems. They have made effective use of shared microscope facilities, to the benefit of their own work as well as to the development of this shared resource at Pasteur. Their work is well integrated within the Institut, with collaborations within and outside the Department of Immunology. The structure of the group (a PI with two senior scientists directing the individual project areas) is efficient and productive. They have been very productive given the size of the unit, and would likely be more productive if allowed to grow (see Recommendations).

- Appreciation on the project

The proposed research program is exciting and combines projects to better understand T cell function and signaling at the cell biological and biochemical level with projects to better define mechanisms of virus infection and control.

1a. Molecular mechanism coupling ezrin with microtubule networks. Work will continue on the mechanism by which ezrin participates in the movement of clusters of signaling molecules within the T cell synapse following TCR triggering to effect signal extinction. This project will make effective and innovative use of multiphoton microscopy of planar membranes to document the localization of the various protein components, with and without silencing of individual proteins. These experiments are potentially very exciting and are expected to provide a highly detailed picture of the signaling characteristics of the T cell synapse.

1b. Role of the signaling scaffold protein SLP-76 and the HPK1 kinase in the regulation of signaling complex dynamics at the synapse and in the downregulation of T cell receptor signaling. SLP-76 was identified as an ezrin interacting partner and its phosphorylation by HPK-1 is involved in negative regulation of signaling. Phosphoproteomic approaches will be used to determine phosphorylation targets on SLP-76 as well as on accessory molecules, and their role in signaling will be examined by site-directed mutagenesis, testing the hypothesis that adhesion or co-stimulatory proteins are modulated by HPK-1 during signaling.

Project 1, a continuing collaboration with the laboratory of a former member of the department, now in Oxford, is expected to produce a precise picture of negative feedback loops that control the intensity of T cell signaling by modulation of immunologic synapse structure. Significantly, this is an area of investigation brought to the group by a senior scientist of the team, and represents an important expansion of focus for the lab.

Project 2. Intracellular vesicle transport targets T cell receptors and signaling molecules to the immunological synapse. Subversion by HIV-1. Previous work exploited the ability of HIV-1 Nef to disrupt T cell synapses by preventing movement of Lck-containing clusters without affecting the movement of LAT. This result was interpreted as evidence that signaling vesicles are heterogeneous, and this hypothesis was confirmed by detailed image analysis. This work will be expanded to determine the regulatory mechanisms of vesicle composition and their interaction with HIV-1, using a combination of imaging and biochemical studies to define vesicle heterogeneity and how viral infection affects synapse formation.

Project 3. Mechanism of HTLV-1 cell-to-cell transmission via biofilm-like extracellular viral assemblies. This project builds on the discovery that HTLV-1 accumulates in extracellular structures that facilitate viral transmission. The molecular mechanisms involved in extracellular viral assemblies will be examined by using RNAi silencing and overexpression of mutant candidates molecules, a number of which have been identified by this laboratory. The novelty of this project and its potential importance were of particular note to the Committee.

Project 4. Role of Tuba in the formation of the immunological and virological synapses and in retrovirus transmission. Tuba was identified by this group as an Env-interacting protein that mediates the effects of HTLV-1 on the T cell synapse. Future work is aimed at understanding how Tuba functions in maturing the assembly of the synapse, mostly by visual comparison of cells expressing or lacking Tuba. These are somewhat open-ended experiments, but they could lead to novel insights of HTLV and HIV infection.

- Recommendations

The Committee considers that this group would benefit from some expansion, to allow greater development of the individual senior scientists and to encourage the interdisciplinary approach of the Unit. An additional PhD student trainee for each of senior scientist would seem appropriate.

The quantitative imaging studies by this group will be expected to produce large data sets that may strain the current IT data storage and bioinformatics capabilities of the Institut. The Committee recommends addressing this infrastructure issue, to the benefit of both the present laboratory and the Department in general.

Title of the team: Développement des tissus lymphoïdes

Name of the team or project leader: Gérard Eberl

- 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)	6	6
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)	0	0
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

The group applied originally for the establishment of a 'G5 group' at the Pasteur with the aim of a better understanding of the biology of lymphoid tissue inducer cells (LTi) which it could visualize in tissues by way of an LTi-specific reporter (RORgt-green fluorescent protein) gene in mice. While the mainstream focus in this field at the time was the role of LTi in the development of secondary lymphoid structures such as lymph nodes and Peyer's patches, Its interest turned to the generation of inducible, so-called "tertiary lymphoid structures" in the gut. Here, small clusters of lymphoid-like progenitor cells had been discovered years ago by researchers in Japan, and these were termed cryptopatches. Subsequent work, largely attributable to the group leader and his colleagues, showed that cryptopatches, and further intestinal structures, termed "isolated lymphoid follicles" are the 'crystallization nuclei' of inflammation-driven tertiary lymphoid tissue formation in the gut. Moreover, their research established which key cell types drive these organogenic reactions and, most impressively, unraveled the molecular cascade that leads from gram-negative bacteria-derived peptidoglycans via an intestinal epithelial receptor (NOD1), and chemokine release to the activation of LTi. Moreover, they have also made significant contributions such as identifying a link of RORgt to NK cell and Th17 immunity.

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

It is fair to say that the recent discoveries reported by this group in top journals have turned the PI into a young leader in this emerging field. The group has achieved a truly remarkable visibility, which, in turn, has case a bright light onto the Institut Pasteur.

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

It is evident from group leader's publications and from his presentation to the Review panel that he is very well connected within and beyond Institut Pasteur and readily establishes productive collaborations in which he mostly maintains the leading role. His standing and visibility is also underscored by the fact that he has contributed several reviews in a timely fashion, which can be expected to be widely read.

- Appreciation on the project

The group is now presenting a new and extensive research program to apply for the formation of a new Unit under his directorship. The future research plan is very interesting, highly ambitious, and extends his ongoing efforts in a very broad manner. The future projects can be grouped into four areas. (1) How do symbiotic microbes activate the intestinal (and possibly systemic?) immune system? (2). What is the nature of the interaction of intestinal

epithelial cells and lymphoid stromal cells? (3) How is intestinal homeostasis disrupted by mutations (of the host) and by infections? (4) How can homeostasis be re-established to control inflammatory diseases? Excellent preliminary data and novel tools were already presented to support the feasibility of these projects. The Review sub-Committee was impressed by the scale, scope and depth of the planned projects, but also raised some concern that shear size and volume may not always translate into proportional output and productivity. This issue was particularly germane to whole-genome sequencing of a multitude of intestinal commensals and pathogens in the context of both wild type and mutant mouse hosts. Nevertheless, the panel was highly positive and strongly recommended the implementation of a research Unity headed by the G5 team leader. His future research has the potential to provide novel and relevant data and to thereby improve our concepts of how benign and pathological intestinal microbes, respectively, influence the formation and regulation of the immune system. This strategy seems to fit beautifully into the broader focus of attention of Institut Pasteur.

Title of the team: Immunorégulation

Name of the team or project leader: Lars Rogge

- 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	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
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)	3	3
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

The group was only recently created in 2002 and then transformed into a Unit in 2007. The group leader joined Pasteur with previous experience in a research lab of a major pharmaceutical company. However, that particular lab in Milan was physically separated from the main company, and developed its own outstanding scientific reputation. Within this, the group leader was a very productive investigator, making well-recognized contributions in the field of mechanisms regulating Th1 cell commitment. The molecular mechanisms of T cell activation and commitment are intensively and aggressively studied in the mouse system by many outstanding investigators, and the field is moving very rapidly. However, there is a clear need for the better characterization of the mechanisms regulating human T cells that are under-studied, and that are at least in part different from those in the mouse. Unlike many descriptive studies in this area, investigations of human T cell commitment and differentiation performed by the group leader are sophisticated, state-of-the-art, and incisive, and his recent studies on the regulation of IL-12Rbeta2 and T-bet are very compelling.

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

The improved knowledge of the human lymphocyte physiology is obviously important for translational studies and for the possible clinical application of more basic principles. By providing such knowledge, this group is regaining an important position in the international immunology community and its planned studies are likely to generate further basic and translational insights. Two recent studies published by the group on the regulation of IL-12Rbeta2

and T-bet in human T cells are of great interest and clearly identify differences between the mouse and humans that may explain some difference in the immunological responses of the two species. This is a very neglected field of research and many of the papers are descriptive at the cellular level, failing to attempt sophisticated molecular analyses of the kind undertaken by this group. The technology applied to these studies is state of the art and the ongoing or proposed studies on the epigenetic control of gene expression in T cells are as sophisticated as the studies underway in the best laboratories studying mouse Th cells. The group is also obtaining interesting data on the regulation of IL-17 and IL-22 production by human T cells, another field in which there is still much confusion both in the mouse and in humans. These studies are likely to further increase his visibility. This group is also involved in several collaborations with other Pasteur investigators, both within and outside the immunology department.

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

After its inception, the group was soon joined by a Staff Scientist who was previously at the San Raffaele Hospital, and who brought to the group an interesting line of research in signal transduction with a particular emphasis on the COP9 signalosome. However, the group is a small one, with one technician and three PhD students, and within this, the presence of two distinct research activities that did not obviously complement each other represented a weakness. This clearly affected the productivity of both investigators. In particular, the COP9 signalosome project did not receive strong support in scientific review, and has given way to an increased focus of the Unit on the regulation of human lymphocyte responses. This has positively affected productivity, and the two recent papers on the regulation of IL-12R and T-bet in human T cells are important, novel contributions to the field. However, within this very competitive field, the group will only maintain its position by working closely together, and harnessing the complementary skill-sets of the two lead-investigators on a focused line of investigation. Importantly, this seems to have been well-recognised by the Group, and the Scientific Review Committee therefore commends the group leader on his management of a challenging situation, and his rejuvenation of the group's productivity.

The group also seems to be very involved in training. The group leader teaches at the university and he has trained 4 PhD students, 4 master students, and one postdoc. It is also very important to note that the group leader has provided very strong support in the development and management of the CIH. This is a very worthwhile effort that will increase his interactions and collaborations with other groups at Pasteur and with clinical researchers in Paris and throughout France. This Center should greatly aid the work of the Unit.

- Appreciation on the project

In the four year plan, the group is putting more emphasis in some translational projects, in particular the characterization of the Th1/17 cells in ankylosing spondylitis and in Crohn's disease, with particular attention to the role of IL-23 variants in the regulation of Th cells. It also proposes some more molecular studies to define the epigenomes of differentiating and established human Th1 and Th17 subset. Also, he will study the role in Treg cells of a newly identified forked domain transcription factor, FOXL, that may be more specifically expressed in human Treg cells than FOXP3. These latter studies will utilize both human material and newly established mouse models. Overall this is an impressive and focused research plan, strengthened by a good balance between basic investigation and more translational ones. The potential impact of these lines of investigation is quite high. At the present the overall quality of this research program is very good. However, after a period of relatively modest productivity, this group has produced some quite exciting findings that have resulted in a few high level publications. Thus, after a relatively slow start, this small group is now progressing very well, and the proposed plan and the potential for the next four years can be defined excellent.

- Recommendations

A moderate expansion of the group size would allow it to grow scientifically and remain productive in this competitive field.

Title of the team: Vaccinologie parasitaire

Name of the team or project leader: Shirley Longacre

(has been evaluated by another committee, in the context of 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
Non noté	Non noté	Non noté	Non noté	Non noté

Nom de l'équipe : BIOLOGIE CELLULAIRE DES LYMPHOCYTES - URA 1961

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 TISSUS LYMPHOÏDES

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 : BIOLOGIE DES POPULATIONS LYMPHOCYTAIRES URA961

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 : SIGNALISATION DES CYTOKINES

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	B	A	A+	A

Nom de l'équipe : IMMUNORÉGULATION

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+

Alain Israël
Directeur de l'évaluation scientifique

Le 16 avril 2010

INSTITUT PASTEUR

25 rue du Dr Roux
75724 Paris Cedex 15
FRANCE

Email : aisrael@pasteur.fr

AERES

Antonio Freitas, directeur de l'URA CNRS 1961, n'a pas d'observations à apporter concernant le rapport d'évaluation de l'AERES (ni de report d'erreurs factuelles).

Alain Israël
Directeur de l'Evaluation scientifique