Régulation immunitaire et vaccinologie

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Immune regulation and vaccinology unit

From the

INSERM

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: Immune regulation and vaccinology

Requested label: UMR_S

N° in the case of renewal: 883

Name of the director: Ms. Claude LECLERC

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. Pet BRANDTZAEG, Oslo, Norway

Mr. Bruno LUCAS, Paris, France

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

Ms. Danila VALMORI, Nantes, INSERM CSS member

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 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)	1	1
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)	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)	4	1
N7: Number of staff members with a HDR or a similar grade	3	3

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	5
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	5/5
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

The group has been consistently productive over a long time period. It has published over 40 papers in the last 4 years in well respected peer reviewed journals and 5 review articles. Perhaps most importantly it has recently made some very exciting observations that has led their research, in part, into the very exciting area of cancer vaccines and they established the infrastructure to pursue the translation of these findings into potential human immunotherapies against cancer by forming strong alliances with the Ludwig Institute for Cancer Research and with companies interested not only in pursing unique vaccine targeting systems but also who are willing to perform the complex monitoring needed to run such clinical trials.

- 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 held in very high regard by the international immunology community. She or members of her group are consistently invited to present in national and international scientific meetings (such as the Joint Meeting of European National Societies of Immunology, the International Conference on Immunotherapy and Immunomonitoring and the European Workshop on Bacterial Protein Toxins). She and members of her group are frequently sought-after participants in institutional seminars and Gordon conferences, frequently teach in courses and she has been a co-organizer of Vaccinology Colloquium for the past three years. The lab is well funded.

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

The group has assembled and obtained funding for a large research team. These efforts have permitted them to pursue, in part, translational aspects of her interests in vaccinology especially for cancer. In that regards a wonderful job has been done establishing the infrastructure needed to perform these studies. On the other hand, the interests of the group have clearly become quite unfocussed in the intervening years. While several aspects of the research are interesting, it is not clear how they tie together. Moreover, the Scientific Review Committee was unconvinced that the expertise of some of the group members is appropriate to pursue some of their proposed studies in fields that are extremely competitive and already populated by well-established, highly productive investigators. In short, the Review Committee expresses a significant level of concern that the group has lost focus and thus has outgrown its capacity to function as a cohesive research group. The group leader may need to spend time reorganizing the group to bring the focus back in line with her own major research interests.

- Appreciation on the project

The proposed research program has both strengths and weaknesses. There is enthusiasm for the plans to pursue the translational and clinical aspects of the very novel vaccine strategies that the group leader has proposed. The data provided are extremely convincing and exciting. This work couples nicely with the group leader's profound understanding of dendritic cell biology, and represents a direct outgrowth of years of high quality work by her group. The opportunities that her new vaccines offer in cancer therapy are extremely exciting and the committee supported the efforts to pursue the translational aspects of this work vigorously. The group leader is the obvious person to lead this effort.

In addition, the work on neonatal immune dysfunction was exciting, with unexpected insights into mechanism. The responsible scientist has done a superb job with this project and has in the process established himself as a leader in this field, publishing in first rate journals and obtaining funding to pursue forward-thinking projects. Again, the committee enthusiastically supported further exploration basic mechanisms at play in this system.

On the other hand, the committee had significant concern about some of the other areas of the proposed research. In the case of the project on plasmacytoid dendritic cells, there is significant worry that the tumor models (tumor cells generated many years ago, propagated many times in vitro, and that are then engineered to express ovalbumin as a model tumor antigen) are highly artificial and in many circles no longer accepted as suitable cancer models. Moreover, the data that support this project and the rationale underlying the project were not particularly convincing.

The proposed T-reg project is in its infancy, lacks supporting data and there is concern that the project will not be competitive in light of the extremely vigorous international effort being expended on T-regs by large and mature research teams that are the leaders in the field.

Finally, the TB vaccine project, while important, seems somewhat confused as to whether its focus should be on basic microbial pathogenesis or on developing a strategy to vaccinate against TB (a goal that has proven to be extremely difficult in the past). Moreover, this time- and energy-consuming project appears to be less well integrated into the overall efforts of the Unit.

In sum, the committee felt that this is a highly productive unit with a bright future in vaccine development, particularly against tumour targets. However, more effort should be devoted to focusing the efforts of the various investigators in the unit. Only an integrated working environment will prove competitive in a highly competitive area of immunology. Until it functions as a more effective and cohesive Unit, there is no justification for its expansion. Finally, the Scientific Review Committee noted that this Unit might make greater contributions to and derive significant benefits from the CIH.

- Recommendations

The priority is to re-evaluate the Unit organization, as described, so as to promote the effectiveness of the conspicuous strength's of the Unit's endeavours.

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	A	A+	B	A

120ème anniversaire
Institut Pasteur

Unité de Régulation Immunitaire et Vaccinologie

INSERM U 883

Paris, April 15, 2010

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Comments on the report: EVAL-0755366A-S2110044789-UR-RPRELIM

We thank the Committee for evaluating our Unit and for their advices. Although we fully appreciate the time required for the evaluation of the Department of Immunology, we would like however to express our frustration on the organization of the evaluation. Indeed, while the evaluation Committee was composed of prestigious scientists, the time devoted to presentation and discussion by our Unit was limited to only 65 mn (50 minutes presentation and 15 mn discussion) and did not allow a proper evaluation of our activities. Moreover, some of the topics that we are studying, such as the anti-mycobacterial immunity, are relatively far from the scope of expertise of the Committee members. Our feeling is that these topics were not appropriately evaluated. Importantly, no time was planned for separate discussions between the Committee and the group leader or between the Committee and the team members. We firmly believe that issues raised by the Committee would have found appropriate answers if necessary time for discussion would have been allocated. Finally, we do not understand how the management of the Unit has been evaluated by the Committee, without any specific discussions with the group leader and team members, therefore lacking critical insights.

General comments

We would like to point out that our Unit (with a total of 16 members) has been very successful, as noticed by the Committee. The scientific management criticisms are not in accordance with the important and successful achievements revealed by the Committee, which are, for the last four years, as follows:

- 40 publications (with many articles in high impact journals such as Immunity, J. Exp Med, Blood, Cancer Res…) and 5 reviews.
- Eight patents with three licences.
- The creation of one start-up company (Genticel, formerly BT Pharma) based on our CyaA technology, which raised 13.1 million Euros in additional funding in March 2010.
- Three clinical trials under organization, with two starting in 2010. Two of these clinical trials are organized directly by our team.
- Excellent level of funding at the international and national levels.

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It seems that our ranking did not take into account all these indicators. These achievements have been made possible only due the complementarity of our team members with dedicated expertise in various fields as well as the strong cohesion and organisation of the research work. We are deeply convinced that our activities in publication, valorisation and translational research should have been better recognized by the Committee. We think in particular that the Committee may have underestimated our high productivity in valorisation, a field, which is strategic at the national level. They may have also underestimated the amount of resources that were required for our translational research, including setting up methods for GMP batch production, performing potency tests and stability studies, as well as organizing regulatory toxicology studies. This was extremely time consuming for some members of the Unit while these studies are not publishable.

The scientific strategy of our team is based for many years on a very defined and well-organized integration of fundamental research allowing publication in high standard journals, together with more applied research, bringing innovative technologies towards clinical trials. This is a very complex exercise, in which we think we have been quite successful.

The main criticism of the Committee concerns the organization of the Unit with the conclusions that *"the group has lost focus and thus has outgrown its capacity to function as a cohesive research group"*, « *The priority is to re-evaluate the Unit organization, as described, so as to promote the effectiveness of the conspicuous strength's of the Unit's endeavours*" and *"The group leader may need to spend time reorganizing the group to bring the focus back in line with her own major research interests"*.

We respectfully, but firmly, disagree with these conclusions. Our current projects are directly in line with those proposed by our team four years ago when our Unit was re-created, and which received the strong support of the Evaluation Committee. In contrast to the conclusions of the present Committee, we have over the last years progressively increased our focus on tumor immunology and anti-cancer vaccines and abandoned some side projects. Indeed, we share the conclusions of the Committee on the strong potential of our work on tumor immunotherapy. However, as we have demonstrated in large tumor models, the development of efficient anti-cancer vaccines needs a better understanding and manipulation of immunoregulatory mechanisms, including Treg, which develop during the tumor growth. Although highly competitive, the field of Treg, cannot be considered anymore only as specialized topic and a better understanding of the role of these cells in tumor immunity is clearly needed.

Finally, as vaccinologists, we decided more than 10 years ago to introduce an infectious model in our team to develop new vaccine approaches using microbial antigens (and not chicken ovalbumin as most groups are doing). Our expertise in mycobacteria has been, and is still, essential in the development of new vectors such as CyaA or of adjuvant for neonates. Our work in this field had been constantly very productive and in the last four years, has led to articles in high impact journals (including an article in Immunity in 2009 and a patent filled on December 2009, after the evaluation). Finally, it is important to mention that we are working in very close synergy with the group of Roland Brosch, an expert in the genomic of mycobacteria, at the Pasteur Institute. We are the only group at Pasteur mastering the analysis of immune responses against mycobacterial infection. Considering the strategic importance of research on tuberculosis in our Institute, we strongly feel that our activity in this field is essential not only for our group, but also for the Pasteur Institute.

Specific comments

We provide below a point-by-point response to the criticisms on some of our projects.

Comments of the Committee: In the case of the project on plasmacytoid dendritic cells, there is significant worry that the tumor models (tumor cells generated many years ago, propagated many times in vitro, and that are then engineered to express ovalbumin as a model tumor antigen) are highly artificial and in many circles no longer accepted as suitable cancer models. Moreover, the data that support this project and the rationale underlying the project were not particularly convincing.

Our work on pDC is fully integrated into the analysis of the dendritic cell biology that we started 15 years ago and which has been always very well evaluated by the various Committees. In the last few years, we decided to better integrate it into our program on the development of anti-tumor immunotherapy. The rational of this project is based on the increasing evidence that pDC could play an important role in the host-tumor interaction. The characterization of the role of pDC in tumor immunity is a very important and open question, although still highly controversial. We decided that the best way to address this question is to develop a mouse model lacking pDC. This was a long and risky project but we were successful and obtained these mice few months ago. An article describing this new model will be send to publication quite soon. Our aim is now to use this mouse model to characterize the role of pDC in cancer development, based on different tumor models. We strongly think that our work will be very competitive since the other mouse models under development are less appropriate for such studies. We fully agree with the Committee that tumor models expressing OVA are artificial. But OVA specific tools (hybridomas, transgenic mice) represent an unique approach for some studies concerning the role of pDC on the induction of class I or II restricted immune responses. Every tool has its own advantages and limits and it is obvious that relevant tumor models (that we are using routinely in the laboratory) will be used for more physiological questions. In fact, our experiments with "real tumors" in these mice lacking pDC have already started.

Comments of the Committee: "The proposed T-reg project is in its infancy, lacks supporting data and there is concern that the project will not be competitive in light of the extremely vigorous international effort being expended on T-regs by large and mature research teams that are the leaders in the field".

We fully agree that the proposed Treg project is still in infancy since the member of the team who will develop it has been recruited by INSERM to work on this project only in October 2009. It could have been a mistake to present a short description of this project but as discussed above, we think that successful immunotherapy will be developed only with a better understanding of mechanisms that suppress the induction of efficient immune responses. Treg represent an important component of such a strategy. So far, most studies on Treg in cancer patients or experimental tumor models have been mostly descriptive. Our objective is to understand the origin of tumor Treg and to develop new strategies to overcome their suppressive property. In the past decades, most therapeutic strategies have been focused simply on Treg depletion by non-specific antibodies or chemical reagents, leading to controversial and disappointing results. A better understanding of the physiology of tumor Treg cells, especially their origin and their interaction with other suppressor cells, is thus clearly needed. The young scientist recently recruited in our group on this topic has been working in a world's leading Treg lab for 4 years and has published several seminal papers on the regulation of Treg cells in peripheral tissues. We are thus confident that our project will provide

important information on the properties of tumor Treg cells and will contribute to the development of better therapeutic strategies.

Comments of the Committee: Finally, the TB vaccine project, while important, seems somewhat confused as to whether its focus should be on basic microbial pathogenesis or on developing a strategy to vaccinate against TB (a goal that has proven to be extremely difficult in the past). Moreover, this time- and energy-consuming project appears to be less well integrated into the overall efforts of the Unit.

As mentioned by the Committee, vaccination against TB has proven to be extremely difficult. Thus, as for other pathogens, a better understanding of the host-pathogen interaction is clearly needed and represents the actual approach for TB, as for other pathogens, used by most vaccinologists. Our strategy is based on a very strong and synergistic interaction with the teams of Stewart Cole and Roland Brosch, who are internationally recognized leaders in genomics of mycobacteria. This collaboration has been very fruitful and has led to major publications in the last few years (Nature Medicine, PloS Pathogens...). Besides, as discussed above, this infectious model has been very instrumental for our group to develop new vaccine strategies. Strong interactions indeed exist between this topic and our work on neonatal immunity.

Sincerely yours,

Pr. Claude Leclerc