

Pathogénie microbienne moléculaire

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit

Colonisation et invasion de muqueuses

Pasteur Institute of Paris



November 2008



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Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

November 2008



Evaluation report



The research unit :

Name of the research unit : Colonisation et invasion de muqueuses

Requested label : UMR_S

N° in case of renewal : 389

Head of the research unit : M. Philippe SANSONETTI

Other institutions and research organization:

Pasteur Institute, Paris

Date of the visit :

25 November 2008



Members of the visiting committee

Chairman of the committee :

M. Thomas MEYER, Max Planck Institute for Infection Biology, Berlin, Germany

Other committee members :

M. Etienne PAYS, Université Libre de Bruxelles, Belgium

M. Jacques NEEFJES, The Netherlands Cancer Institute, Amsterdam, The Netherlands

M. Malek DJABALI, Centre d'Immunologie Marseille Luminy, France

Ms. Suzana SALCEDO, Centre d'Immunologie Marseille Luminy, France

Ms. Dominique BUZONI GATEL, Institut National de la Recherche Agronomique, Tours Nouzilly, France

Representative CSS INSERM :

M. Stéphane BONACORSI, Paris

Observers

AERES scientific representative :

M. Stéphane MERESSE, Marseille

INSERM representative :

Ms. Christine TUFFEREAU, Paris



Evaluation Report

1 • Short presentation of the research unit

- Numbers of lab members including researchers with teaching duties, full time researchers, ingeneers, Phd, students, technicians and administrative assistants : 41
- Numbers of HDR and of HDR who are PhD students avisors : 6
- Numbers of PhD students who have obtained their PhD during the past 4 years: 6
- Numbers of PhD students currently present in the research unit : 7, all with felowship
- Numbers of lab members who have been granted a PEDR : 1
- Numbers of “publishing” lab members : 37

2 • Overall appreciation of the activity of the research unit, of its links with local, national and international partners

General comments

The report provided for the AERES evaluation well reflected the wealth of excellent research done in Unit U786 at the Institut Pasteur. It highlighted all relevant information required for the committee to evaluate the concluded and concurrent research programs, as well as the goals for the next 5 years. The presentations given by members of the unit were scientifically insightful and engaging. Stimulating, open and enthusiastic discussions ensued between presenters and audience that were enjoyed by all present.

The Unit

Unit U786, including 2 teams, was established at the renowned Institut Pasteur in 2006. The two teams have carried out excellent work at the interphase of pathogen-host cell interactions, which has led to a series of outstanding observations for the respective pathogens. Projects performed and presented were of high scientific quality and originality and provide significant contributions to the advancement of infectious disease research. In most cases, the projects represented a logical continuation and extension of previously started work; this is not only true for the basic research fields, but also concerning the development of diagnostic tools and vaccines. Moreover, the implementation of new research projects, such as the study of gut homeostasis, hold promise for future discoveries. Access to unique technical platforms (e.g. animal facilities, imaging, bio-informatics) that are both crucial and enormously helpful for the proper development of the conducted projects is provided by the host institute. In addition, the numerous researchers within the Unit are involved in many collaborations both within as well as external to the Institut Pasteur, thereby facilitating project progress by providing access to additional technical skills, equipment and intellectual input.

The review committee experienced a highly motivated group of Principal Investigators (PI), post-doctoral researchers and Ph.D. students, of many different nationalities and cultures, and wholeheartedly appreciated the scientific discussions during the site visit. The post-doctoral researchers and Ph.D. students seem to be genuinely happy with the working environment and their research programs; after discussions with them the following recommendation were made:

1. The Ph.D. students appreciated their tutor for annual discussions about work progress and other relevant items. However, they would favor the installation of evaluation committees with PI's from other groups in or external to the Institut Pasteur to achieve a more in-depth and unbiased discussion of their scientific progress.



2. The post-doctoral researchers were generally pleased about the research facilities at the Institut Pasteur. Yet, they expressed concern that particular facilities were often overbooked. In particular, the imaging facility with confocal and bi-photon microscopes is heavily in demand. The committee thus recommends allocation of appropriate funds for the acquisition of a bi-photon microscope - an important part of modern equipment for state-of-the-art imaging. The committee is aware that the acquisition of such equipment will also require special funding for the daily maintenance. Under the current situation this poses a significant bottleneck of scientific progress in the Unit.

3. The “technician and ingénieur” group enjoys working for the teams and appreciates current access to additional training provided by the Unit. Although no particular concerns regarding work conditions were expressed, they would appreciate an opportunity to discuss, well in advance of Group Leaders departure, what they will do and where they will be dispatched once both are retired.

A minor concern raised about the Unit was the lack of significant collaboration between the two teams, mostly due to their physical separation in the current building. At present, weekly/fortnightly laboratory meetings are providing some opportunity for more interaction between the two teams; however, the committee is convinced that the impending relocation of both teams into the same laboratory area in the coming year will further stimulate the truly needed productive scientific interactions.

Taking all points into consideration, the review committee has attributed the Unit U786 an overall top ranking. This laboratory constitutes an outstanding international leadership in the field of infection biology and the proposed work program is likely to foster this position. The Team 2 look set to improve upon previous merits with the development of RNA interference (RNAi) for the amoeba *Entamoeba histolytica*, which will allow an analysis of the molecular basis of this pathogen’s behaviour and should lead to publications in high-ranking scientific journals. Interaction between the two teams will be instrumental in achieving this goal.

3 • Specific appreciation team by team and/or project by project

Team 1

The overall scientific quality of this laboratory is outstanding. It has reached and in some cases surpassed the goals proposed in the previous evaluation. In the past 5 years this laboratory has been at the leading front of bacterial pathogenesis research in the fields of both cellular microbiology and host immune response. The team has significantly contributed to the advancement of bacterial pathogenesis research by pursuing novel projects, such as the epigenetic regulation of pro-inflammatory genes, which are proving to be common themes in the control of the immune response by many pathogens. This innovative force has resulted in several publications in prestigious journals, such as *Science*, *Nature Immunology*, *Journal of Experimental Medicine* and *Immunity*, several patents and numerous presentations at highly regarded scientific meetings.

The proposed research projects for the next 5 years are ambitious, original and will further advance the field of microbial pathogenesis. Two most promising themes are emerging: first, the characterization of commensal bacteria populations in the intestine, particularly the crypt; this project, which is presently highly debated among the scientific community, will study their impact on the developmental biology of the intestinal tissue as well as understand their interplay with bacterial pathogens, namely *Shigella*. Second, the study of epigenetic regulation of immune innate genes during *Shigella* infection should provide unifying ideas on the subversion of the immune system by pathogens and will continue to aid the development of new vaccine and treatment strategies. The development of this project is also based on strong collaborations with well established “epigenetic laboratories”. In addition increased emphasis is also being placed on the infection of the lung by *Klebsiella pneumoniae*, a project that will involve sophisticated imaging technologies.

The team has been very successful in training and promoting young research scientists, as demonstrated by the numerous post-doctoral and senior researchers that now pursue their own independent research careers. The review committee was genuinely impressed by the quality and breadth of the work presented. The perspectives of future research in the team concerning five major areas, i.e. search for type III secretion effectors, epigenetic modulation, adaptive immunity, the new *K. pneumoniae* model and gut homeostasis and colonization is likely to provide fascinating and rewarding new insights. The intended addition of studies involving axenic mice would be costly and time consuming; however, the committee believes such studies could add a crucial dimension to the understanding of infections *in vivo* and supports this risky effort as well. Altogether, the intended research approach of the team 1 is promising and important new insights and discoveries are likely to

result from the team's activity.



| 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+ |

Team 2

The team 2 has achieved an overall very good ranking. This team has successfully embarked in a relatively unique, yet, considerably relevant infection model in the neglected field of *E. histolytica* biology. On this basis, they have regularly published good papers. During the period 2004-2008, twenty-nine publications in peer-reviewed international journals are reported, some of which in the well-respected *Journal of Cell Science* and *Infection and Immunity*. Recent progress included the identification of novel virulence factors, which could play important functions in invasion and/or immunomodulation of host cells. Importantly, using their newly developed RNAi technology for *E. histolytica* gene silencing, the function of these virulence genes will be identified. The group has also developed an *ex vivo* system on colon explants to study the biological and molecular processes at work during pathogen invasion. Microarrays have been constructed for this purpose, both from the parasite and host cells. Taken together, these investigations have allowed the group to play a significant role in the field, with particular contributions to the molecular dissection of parasite motility and the discovery that inflammatory cytokines such as TNF- α are chemoattractants for *E. histolytica*.

The team includes a number of highly motivated Ph.D. students and post-doctoral researchers who are expected to further benefit from the closer association with the team 1 in the new laboratory space.

The team is now facing an important next step, i.e. the transition from a more descriptive phase towards a more mechanistic understanding of cellular events during these infections. For this purpose they have now established useful analytical tools that will allow the team to better focus on clearly defined (e.g. molecular) questions. The panel felt, however, that the detailed description of the motility process was less likely to produce data favourable for publication in high-impact journals. Identification of the function of new virulence factors and analysis of the inflammatory and immune response elicited during the invasive or chronic phase of the disease, could bring some new insights for a better understanding of physiopathological mechanisms and lead to novel therapeutic strategies. These more mechanistic types of investigations are likely to generate the high-impact findings expected from a group, which has assembled considerable expertise, outstanding collaborators and highly motivated team members.

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|------------------|------------------------------------|---|--|------------------------|
| A | A | A | B | A |



4 • Concluding Remarks

The overall scientific quality of INSERM Unit 786 is outstanding. It has attained an international reputation of the highest level based on excellent research achievements in the field of infectious disease research. The unit pursues a strong research program and deserves full support. The unit is found to be in an optimal condition with regard to both research infrastructure and competence and commitment of employed personnel. Furthermore, the two teams are expected to greatly benefit from their future closer spatial association. Additional advancements could be achieved through implementing a more vigorous Ph.D. program and the acquisition of sophisticated microscopic equipment for the daily use of the teams.

| 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+ | A | A+ |