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

Section des Unités de recherche

Evaluation report

Research unit

Ecosystème Intestinal, Probiotiques, Antibiotiques

University Paris 5



February 2009



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University Paris 5



Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

February 2009



Evaluation report)

The research unit:

Name of the research unit : Ecosystème Intestinal, Probiotiques, Antibiotiques

Requested label : EA

N° in case of renewal : 4065

Head of the research unit : Ms. Marie-José Butel

University or school:

University Paris 5

Date of the visit:

November 14th 2008



Members of the visiting committee

Chairman of the committee:

M. Michel Popoff, Institut Pasteur, Paris

Other committee members:

Ms. Paola Mastrantonio, Istituto Superiore di Sanità, Roma, Italy

M. Michael Blaut, German Institute of Nutrition, Nuthetal, Germany

Ms. Arlette Darfeuille-Michaud, Centre Biomédical de Recherche et de Valorisation, Clermont-Ferrand

M. Ian Poxton, Microbial Pathogenicity Research Laboratory, Edinburgh, UK

M. Michel Arthur, Centre de Recherche des Cordeliers, Paris

Representative:

Mrs. Chantal Finance, Nancy, CNU representative

Observers

AERES scientific representative:

M. Stéphane Méresse, CIML, Marseille

University or school representative:

M. Arnaud Ducruix, University Paris 5



Evaluation report



1 • Short presentation of the research unit

- Total number of lab members : 16 including
 - o 5 researchers with teaching duties
 - o 2 postdoctoral fellows
 - o 4 PhD students, all with fellowship
 - o 2 engineers, technicians and administrative assistants
- Number of HDR : 3
- Number of PhD students who have obtained their PhD during the past 4 years : 5
- Number of lab members with a PEDR : 2
- Numbers of “publishing” lab members : 5 out of 5

2 • Preparation and execution of the visit

This research unit is located at the Faculty of Pharmacy.

A report had been delivered to each review committee member including the organization of the laboratory, the objectives and main results of the activity of the previous period, scientific projects for 2010-2013, and administrative information. This report was clearly presented and gave a detailed overview of the activities of the group. Only the summary was written in English, permitting a limited appreciation by the external review committee members.

The review proceeding was well organized. Five oral presentations by the senior scientists detailed the activities and projects of the team. The quality of the presentations was appreciated by all the review committee members and permitted a frank and friendly discussion with the director, assistant professors, and PhD students. These presentations adequately complemented the written report and clearly exposed the recent results, the methodological strategy used in the laboratory, and the projects. The ensuing discussion between the review committee members and the scientists, students, and laboratory staff was open and gave the impression that the team members are highly motivated.

A weak point was the length of the presentations that were partly redundant (first by the research director and subsequently by the scientists) and left little time for discussion.

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

The team is a young. The Director was recruited in 1992 for teaching and researching activities. The scientists currently present were recruited between 1999 and 2004, and the team received the EA approval from the ministry of Research in 2006 for a four-year period: an initial 2 years followed by 2 further years after an



interim evaluation (miparcours). Since July 2008, the Director is also the head of the Department "Perinatalité, Microbiologie, Drugs" which encompasses 7 research laboratories from the Faculty of Pharmacy. The group is part of the Federal Institute of Research 71 and will be linked to the new IFR (Médicament-Toxicologie-Chimie-Environnement) in collaboration with the University Paris Diderot.

The Director and assistant professors are also involved in teaching for undergraduate and graduate students, as well as to adult education, hospital functions for three researchers, and research activity.

The central theme of research is the intestinal ecosystem, which is subdivided into two main axis: establishment of the bacterial microflora in infant gut and antibiotic resistance in intestinal bacteria.

The production of publications (33) within the past 4 years is satisfactory for a small and young team. The work on antibiotic resistance is regularly published in high level journals, and the publications in the other axis are less strong but improving.

The group is also represented at international level by three invited conferences and at national level by four invited talks.

The laboratory has fruitful and productive collaborations with hospital units as well as with other research teams from the Faculty of Pharmacy and from other French Universities and research organisms such as INRA, and Pasteur Institut. Recently, the Director organized with other colleagues a national network on probiotics.

The work is supported by two ANR projects, multiple industrial contracts, and industrial and association grants for students.

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

The unit members have reported their recent results on the establishment and modulation of the gut microbiota in premature and full term infants, phenotyping, genotyping and proteomic analysis of Bifidobacterium strains, and the role of microbiota in immunostimulation.

In collaboration with hospital neonatal Units, the group studies the intestinal colonization in preterm infants who are at high risk of infection, mainly necrotizing enterocolitis (NEC), and the characterization of the dominant bacteria, essentially Bifidobacterium. The group participates in clinical trials investigating the effects of probiotic strains on the gut microbiota and on prevention of digestive disturbances. In addition, a non-invasive test for early NEC diagnosis based on detection of inflammatory markers in faecal samples is being investigated. This research topic is highly relevant notably in a clinical perspective. It is noteworthy that even the study on this issue started a long time ago in several laboratories, its complexity has not yet permitted a complete comprehensive understanding. The group has introduced a molecular approach to analyse the Bifidobacterium strains and to investigate the colonization mechanism. The team has also expertise in the use of gnotoxenic animal models. In addition, the impact of gut microbiota on immunostimulation and on allergic diseases is also being investigated.

The second research axis, supported by two oral presentations, concerns the transfer of antibiotic resistance between intestinal bacteria such as intra- and inter-species transfer of the vanA gene between Enterococcus, modulation of antibiotic resistance transfer by the presence of Bifidobacterium, emergence of antibiotic resistance in the gut microflora, and emergence and mechanism of resistance to linezolid in Enterococcus. Recent genetic and biochemical methods are used in this study and pertinent results have been obtained.

The research projects are continuing from previous works. The extensive study of the gut microbiota, NEC, and bifidobacteria will be supported by the Premaflora grant (2008-2011) from ANR, in collaboration with 6 other



teams. The second axis of research includes the investigation of the emergence of resistance to linezolid in infants treated with this antibiotic and in a gnotoxenic animal model as well as the mechanism of resistance to linezolid.

5 • Appreciation of resources and of the life of the research unit

The group consists of one Director, 4 scientists, 2 post-docs, 4 PhD students, lab technicians and administrative staff. In the next period, two new scientists will join the team. Three scientists have an HDR, and in the near future, two additional seniors will have this habilitation.

The contribution to the teaching of students is high, 5 PhD and 1 HDR in the past 4 years. The students, who appear enthusiastic, appreciate the regular and efficient management by the senior scientists.

The team is located in old rooms that have been partially renewed. Additional refurbishment is urgently needed.

6 • Recommendations and advice

— Strong points:

These concern the relevance of the research field: infant gut microbiota and antibiotic resistance. The EA4065 has acquired a recognized expertise in the gut microbiota and the use of gnotoxenic animals, which is important to improve the knowledge in paediatric digestive diseases, and has developed an original work in antibiotic resistance and antibiotic gene transfer between intestinal bacteria. In addition, the group has developed good and fruitful connections with paediatric hospital Units and industry.

— Weak points:

The team is still a small and has perhaps too many projects, notably in the field of microbiota.

Several aspects of the project concern the use of various techniques to study the composition of the gut microbiota. A weak aspect of these studies is their descriptive nature. It seems that a lot of effort is invested in the implementation of new tools (e.g. proteomics) in the unit in the absence of a clear vision of the limitation of the data that will be generated and of their contribution to specific scientific aims.

The research axis concerning the mechanisms of antibiotic resistance and the dissemination of resistance genes is scientifically sound and has recently led to important publications in good journals. Unfortunately, the resources devoted to this research axis in the unit do not appear to be sufficient to allow its real development. The danger appears here that the group shifts from one project to another, at the scale of a single publication, without really building a strong research axis over time. The recommendation is to devote more resources to this research axis. Even though the research axis is not highly integrated into the other projects, it seems that the expertise on antibiotic resistance and gene transfer should be of benefit for the entire team.

— Recommendations:

The team has made great efforts in developing their research on the gut microbiota and the transfer of antibiotic resistance. The originality of these studies, supported by young and dynamic scientists, should lead



to pertinent results in the next period. The team should be supported because of the importance of the research field and its potential direct implications in clinical paediatrics. Many grants come from industrial sources, which might negatively impact research projects. For a more productive research activity, the team should focus on a more limited number of specific aims.

| Note de l'unité | Qualité scientifique et production | Rayonnement et attractivité, intégration dans l'environnement | Stratégie, gouvernance et vie du laboratoire | Appréciation du projet |
|-----------------|------------------------------------|---|--|------------------------|
| B | B | B | A | B |

Le Président
Axel KAHN

Paris, le 30 mars 2009

DRED 09/n° 109

Monsieur Pierre GLORIEUX
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport de comité de visite concernant l'équipe d'accueil «EA 4065 Ecosystème intestinal, probiotiques, antibiotiques» rattachée à mon établissement.

L'Université a pris bonne note des remarques du comité de visite et veillera à ce que les recommandations faites soient suivies d'effet.

Je vous prie de croire, Monsieur le Directeur, à l'expression de ma meilleure considération.

Le Président de l'Université



Axel Kahn

Paris, le 25 mars 2009

Professeur Marie-José Butel
Laboratoire de Microbiologie
Equipe Ecosystème intestinal, probiotiques, antibiotiques (EA 4065)

Respons to the report from the visiting committee of AERES

Our team appreciated the comments of the visiting committee and their suggestions. We agree with their overall and specific appreciations and will take into account their advice for the development of our research.

Moreover, they highlights the old age of part of our rooms and suggests additional refurbishment. We are currently working on a project of gathering in a same site in our faculty all research teams belonging to the department "Perinatalité-Microbiologie-Drugs". This will allow the needed refurbishment.



MJ Butel