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# Ecosystème intestinal, probiotiques, antibiotiques

## Rapport Hcéres

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

Department for the evaluation of  
research units

AERES report on unit:

Intestinal ecosystem, probiotics, antibiotics

Under the supervision of the following  
institutions

Université Paris Descartes





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

Research Units Department

President of AERES

**Didier Houssin**

Research Units Department

*Department Head*

**Pierre Glaudes**



# Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).

This score (A+, A, B, C) concerned each of the six criteria defined by the AERES.

NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

**Criterion 1 - C1** : Scientific outputs and quality ;

**Criterion 2 - C2** : Academic reputation and appeal ;

**Criterion 3 - C3** : Interactions with the social, economic and cultural environment ;

**Criterion 4 - C4** : Organisation and life of the institution (or of the team) ;

**Criterion 5 - C5** : Involvement in training through research ;

**Criterion 6 - C6** : Strategy and five-year plan.

With respect to this score, the research unit concerned by this report received the following grades:

- Grading table of the unit: **Intestinal ecosystem, probiotics, antibiotics**

C1	C2	C3	C4	C5	C6
B	B	A	A	A	A



## Evaluation report

Unit name:	Intestinal ecosystem, probiotics, antibiotics
Unit acronym:	
Label requested:	EA
Present no.:	EA 4065
Name of Director (2012-2013):	Ms Marie José BUTEL
Name of Project Leader (2014-2018):	Ms Marie José BUTEL

## Expert committee members

Chair:	Ms Arlette DARFEUILLE-MICHAUD, University of Auvergne
Experts:	Mr Michael BLAUT, University of Nuthetal, Germany Mr Raphaël DUVAL, University of Lorraine (CNU representative) Ms Corinne GRANGETTE, University of Lille Nord de France Mr Julian MARCHESI, University of Cardiff, UK Mr Ian POXTON, University of Endinburgh, UK

Scientific delegate representing the AERES:

Ms Sophie de BENTZMANN

Representative(s) of the unit's supervising institutions and bodies:

Mr Stefano MARULLO, University Paris Descartes



## 1 • Introduction

### History and geographical location of the unit

The team was set up in the faculty of pharmacy between 1996 and 1999 and was first evaluated by the French ministry of research in 2006 and the unit was renewed in 2010 as EA4065 at Paris 5.

### Management team:

The unit, EA4065, is directed by Professor Marie-José BUTEL and co-directed by Professor Jean-Louis PONS and comprises seven permanent professors and assistant professors with teaching duties, three of whom also have hospital positions.

### AERES nomenclature

SVE1, LS6

### Unit workforce:

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
<b>N1:</b> Permanent professors and similar positions	7 (3) <sup>*</sup>	8 (3.5)	7 (3)
<b>N2:</b> Permanent researchers from Institutions and similar positions			
<b>N3:</b> Other permanent staff (without research duties)	7 (3)	11 (5.8)	3 (1.6)
<b>N4:</b> Other professors (Emeritus Professor, on-contract Professor, etc.)			
<b>N5:</b> Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)			
<b>N6:</b> Other contractual staff (without research duties)	1 (0.2)		0
<b>TOTAL N1 to N6</b>	15	19	10
<b>Percentage of producers</b>	<b>100%</b>		

\* Numbers in brackets = Full-time equivalent



Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	0	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit*	1	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	5	

## 2 • Assessment of the unit

The unit is well integrated into the scientific policy of the Faculty of Pharmacy department “Perinatology, Microbiology, Drug” which encompasses the Inserm unit U767 “Normal and pathologic pregnancy” and the UMR 216 IRD “Mother and child faced tropical infections” and the Hospital University Department (DHU) “Risk and Pregnancy”. The Faculty of Pharmacy has proven to be supportive for the unit as shown by the appointment of a professor (PU-PH) and of an assistant professor with hospital position (MCU-PH) recruited in 2013. For the next five year contract period, a research group comprising a professor, a research engineer and an assistant-engineer from the Conservatoire National des Arts et métiers will join the unit.

### Strengths and opportunities:

The research focus of the unit, EA4065, is on intestinal microbiota in preterm infants. This focus was considered to be an under studied niche and the association of clinicians and basic researchers promises a high probability of success. The Unit provided a research plan for the forthcoming 5 year period (2014-2018) and has made key strategic decisions and alliances that should enable them to start to ramp up their research and make a significant impact in the area of neonatal gut microbiology. The location of the unit at the Faculty of Pharmacy Paris 5, is near other eminent research centres including the Necker, The Pasteur Institute, Paris XI, and Micalis at Jouy en Josas, whose proximity will facilitate collaborations with eminent colleagues in the field at Micalis, at Necker or at Pasteur Institute. These collaborative links will increase opportunities to the Unit to become a global force in neonatal gut microbiology and make a significant impact in this field. Considering its size and composition, the team has been dynamic and successful in obtaining grants from public sources, such as with the highly competitive funding agency ANR, and from private organisations, such as Danone or Nestlé. The Unit has shown a good track record of publications (42 rank A publications) considering the level of manpower in the Unit and the heavy teaching load.

### Weaknesses and threats:

The Unit has certain weaknesses, already identified by the research unit itself or highlighted by the expert panel:

- The publication record, in terms of the numbers of primary publications is good when compared to their peers and taking into account the relatively low number of fulltime researchers. However, the impact and H index are lower than those of other colleagues working in the field, probably due to the heavy teaching duties of the members of the unit, the absence of permanent researchers, and the number of projects being currently run in the Unit simultaneously. Due to the limited size of the unit, some of the results are often descriptive rather than mechanistic.

- The Unit has been slow in adopting Next Generation Sequencing approaches and this has recently led to the establishment of a strategic alliance with INRA at Jouy-en-Josas. However, the expert panel identified the need to clarify who will take the lead in any high impact publications originating from this collaboration.



- There is currently a lack of PhD students and researchers with postdoctoral position in the unit, despite the level of funding and the number of researchers with HDR. Of note, two researchers were recently awarded HDR status. The unit should benefit from the connection with the “Conservatoire National des Arts et Métiers” in their recruitment of good students and engineers.

#### Recommendations:

There is currently not enough in-depth research focusing on several high-impact topics. The unit is advised to strategically choose several interesting research questions/hypotheses in order, according to the small size of the unit, to undertake a much more in-depth research program to gain more mechanistic insights. In agreement with the proposal of the unit itself, the expert panel strongly encourages the researchers to rapidly embed genomic approaches (high throughput sequencing and concomitant bioinformatics) in their research, This focus will allow the unit to develop their own global approaches for a better understanding of the infant gut microbiota, to become a leader in the field of neonatal gut microbiota, increase their visibility in future papers and become much more attractive to facilitate the recruitment of PhD and post doctoral scientists of high quality.

### 3 • Detailed assessments

#### Assessment of scientific quality and outputs:

The main theme of the unit is the ecology of the GI tract of neonates, ranging from establishment of the microbiota of preterm infants, to its role in enteropathies and immunostimulation/allergies. The quality of the research performed, in the context of the intestinal microbiota establishment in preterm neonates and the relationship in health and diseases, is considered to be quite good/satisfactory and they have developed a significant presence in this field of research, with a central position within a department that offers all the facilities to perform clinical trials and to have access to infant cohorts. The experimental approaches are good. The Unit has integrated animal models in their research to validate their observations and evaluate the role of the microbiota and probiotics. The science that has been undertaken is deemed to be of a robust nature and of good quality. The output is good, with a total from 2006 to 2012 of 38 original articles in good international journals (like Anaerobe, Applied and Environmental microbiology) with mean impact factor 3.6; 27 of them directly originated from the research done in the unit and 10 generated from collaborations. The unit also gave 22 oral and poster presentations at national and international meetings and 12 invited talks mostly at the national level. The group has several collaborations with national partners. The quality and quantity of the external funding is good.

#### Assessment of the unit's academic reputation and appeal:

The research projects of the unit are concerned with a medically important field, and the number of research units developing projects in this area is limited worldwide. The unit has a good national visibility through collaborations with neonatal hospital units leading to ANR funded projects “Preamflora” and “Epiflore” and involvement in the national network “Probiotics”, is well-known for its expertise in gut microbiology of neonates and in the field of Bifidobacteria. The unit has many collaborations, mostly at the national level. There is evidence that the unit is capable of acquiring significant research funds from national academic funding organisations and from globally recognized international companies. The unit is involved in several national networks related to different aspects of their work. It has a good reputation at the national level as evidenced from publications and ongoing collaborations.

#### Assessment of the unit's interaction with the social, economic and cultural environment

The unit is well integrated into the scientific policy of the Faculty of Pharmacy Department of “Perinatology, Microbiology, Drug” encompassing the Inserm unit U767 “Normal and pathologic pregnancy” and the UMR 216 IRD “Mother and child faced tropical infections” and the Hospital University Department (DHU) “Risk and Pregnancy”. The main interactions appear to be with clinical units, especially neonatal and maternity units. There is a good backup to the clinic units with dissemination of information to health staff. Evidence was provided of good relationships with industry, mostly with manufacturers of infant formulas and probiotics. The senior staff regularly provides lectures to outside groups. Popular public via popular public scientific publications and press conference provide evidence for the unit effort to disseminate their results to the lay community.





### Assessment of the unit's organisation and life:

Despite the fact that the unit is located at two different sites, this is a small collegiate unit with regular formal meetings. All the staff attends 3 meetings per month during which scientific results and operational aspects of the team are discussed. One researcher takes care of health and safety issues and measures are taken that the projects are done in accordance with ethical regulations. Three researchers are authorized to conduct animal experiments. New knowledge and new skills are entering this Unit. Members of the lab are very supportive of the leader of the unit.

The projects are divided in 3 axes, two concerning the microbiota in neonates (establishment and maturation) and the third one aims to evaluate the role of the cell wall in bifidobacteria and clostridia. The latest project is linked to the expertise of a scientist who joined the team very recently. Interestingly, there is no close separation between the different axes since researchers contribute to the different axis.

### Assessment of the unit's involvement in training through research

Members are deeply involved in teaching at different levels of school of Pharmacy and in Master degree. The unit welcomes a significant proportion of Master students, mainly at the M1 level. There are only a few PhD students but their number will probably increase in the next contract with the increased number of HDR recently defended.

### Assessment of the five-year plan and strategy

The planned future research is a logical step forward from previous findings. The research is organized as three axes.

In the first axis, they plan to continue to study the microbiota composition of neonates. They will have access to a French multicentric cohort of infants that will be followed up for 12 years (EPIFLORE) allowing evaluation of the relationship between the microbiota establishment in neonates, the early perinatal factors and the diseases occurring during childhood. As part of this axis, the Unit plans to specifically evaluate the genotypic diversity of bifidobacteria and clostridia, in samples collected from the cohort previously set up (PREMAFLORA). The aim is of considerable scientific interest, but the readouts and deliverables are not clearly defined. Finally, they plan to investigate the microbiota composition of infants suffering from necrotizing enterocolitis NEC and to evaluate the involvement of bacteria in this disease. In that context, they will also focus on the role of clostridia in NEC by studying the effect of a specific strain and mutants in an animal model. They have also selected a bifidobacterial strain with potential probiotic characteristics, as it is able to protect against NEC in an animal model. They plan to study the effect of this strain in neonates in collaboration with an industrial partner and a pediatrician at the Necker-Enfants Malades hospital. In light of preliminary positive results, this should pave the way for interesting commercial benefits, but also for fundamental research to better understand the mechanism(s) of action.

In the second axis, they aim to decipher the impact of the microbiota on the development of the intestinal immune system. They notably focused their study on allergic diseases. They plan first to first evaluate the impact of microbiota from allergic infants in a gnotobiotic model of allergy to cow milk ( $\beta$  lactoglobulin). Using such a model, they also plan to evaluate the effect of selected probiotics to attenuate the impact of the allergen. This part is interesting since it will allow more mechanistic studies to be performed, but should require a full-time researcher (work intensive model). It also requires good expertise in immunology, notably to evaluate the local immune responses (purification of cells from lamina propria, cytometry, etc...). They also plan to evaluate the faecal eosinophil-derived neurotoxin (EDN) as a potential biomarker of food allergy using a large cohort of infants. This is a small study that could, however, lead to interesting outcomes. The impact of the microbiota will also be evaluated in respiratory allergy in a large scale epidemiological study (from a cohort in Paris).

The third axis aims to evaluate the dynamics of the cell wall in bifidobacteria and clostridia. This is a new research theme linked to the expertise of a researcher (PU-PH) joining the unit. Through the construction of mutants, they plan to evaluate the role of cell wall components in the pro-inflammatory and virulence activities of clostridial strains. The role of cell wall components of bifidobacteria will be also evaluated using in vitro models, in collaboration with a group at INRA.

The research program for the next five-year plan is a wide-ranging and time consuming project considering the size of the unit. To be competitive and to deliver important novel findings, this unit deserves immunologist skills and manpower working on axis 2 of the project.



## 4 • Conduct of the visit

The visit had taken place the 17th December 2012, at the Faculty of Pharmacy, rue de l'Observatoire, Paris Descartes University. After a short closed meeting between the experts and the AERES scientific deputy, the on site evaluation has started at 9:00 and pursued as mentioned in the joined schedule to finish at 16:45. The visit had been carefully prepared and members of the committee appreciated the scientific quality of the oral presentation. During the visit, the informations essential for the understanding of the life of the unit were provided to the panel of experts. The relative contributions of the director, co-director, and of the other members of the team to the oral presentation and to the answers to the questions of the committee were carefully and appropriately planned. An interview with the Vice-President research Paris 5, the Dean of the Faculty of Pharmacy the Director of IFR 71, Sciences du médicament allowed all the experts to evaluate the integration of this Unit in the local tissue.

### Visit date:

**Start:** Monday 17 december 2012 at 9:00

**End:** Monday 17 december 2012 at 16:45

**Visit site(s):** Faculté de Pharmacie

**Institution:** Paris Descartes

**Address:** 4 avenue de l'Observatoire, 75006 Paris

On site AERES visit program  
 Unité Paris5\_PHARMA\_BUTEL\_DESCARTES\_S037  
 Ecosystème intestinal, probiotiques, antibiotiques  
 Intestinal ecosystem, probiotics, antibiotics  
 17 décembre 2012  
 Actual director: Marie-Jo BUTEL  
 Proposed director: Marie-Jo BUTEL

The on site visit will take place at The Faculty of Pharmacy of Paris Descartes University, 4 avenue de l'Observatoire, 75006 Paris

AERES Scientific delegate: Ms Sophie de BENTZMANN

Expert committee: Ms Arlette DARFEUILLE-MICHAUD (Chair) ; Mr Michael BLAUT ; Ms Corinne GRANGETTE ; Mr Julian MARCHESI ; Mr Ian POXTON ; Mr Raphael DUVAL (CNU 87).

9h-9h15	Presentation of AERES visit philosophy and of expert committee by the AERES scientific deputy
9h15-10h15	Presentation of the unit, past activities
10h15-11h00	Presentation of the unit, projects
11h00-11h15	Break
11h15-11h45	Meeting with technical staffs and non-permanents, and permanent researchers
11h50-12h10	Meeting with the director and vice-director
12h10-12h30	Meeting with the supervising institutions and bodies
12h30-13h45	Lunch
13h45-16h45	Closed meeting of the committee



## 5 • Statistics by field: SVE on 10/06/2013

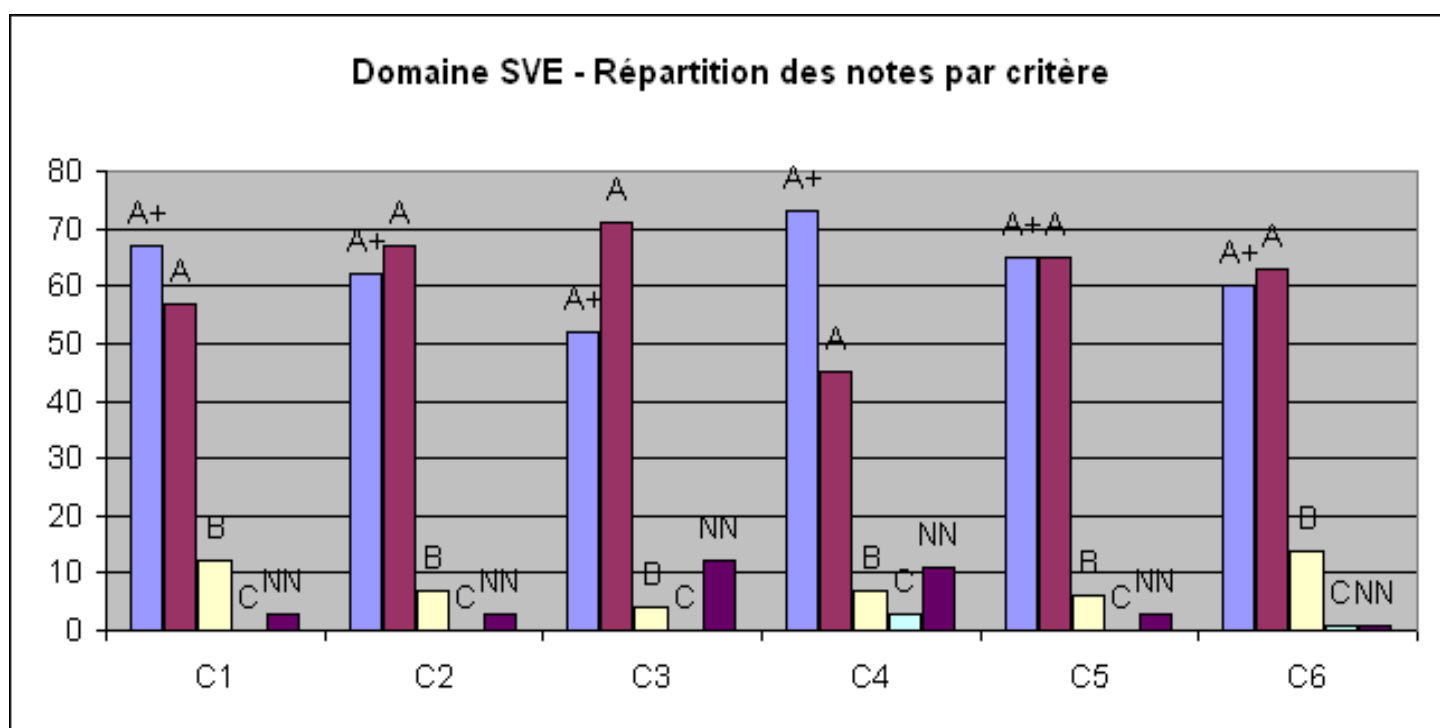
### Grades

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	67	62	52	73	65	60
A	57	67	71	45	65	63
B	12	7	4	7	6	14
C	0	0	0	3	0	1
Non Noté	3	3	12	11	3	1

### Percentages

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	48%	45%	37%	53%	47%	43%
A	41%	48%	51%	32%	47%	45%
B	9%	5%	3%	5%	4%	10%
C	0%	0%	0%	2%	0%	1%
Non Noté	2%	2%	9%	8%	2%	1%

### Histogram





## 6 • Supervising bodies' general comments

Vice Président du Conseil Scientifique

Paris le 26.03.2013

Vos ref : S2PUR140006257 –  
Ecosystème Intestinal, Probiotiques,  
Antibiotiques - 0751721N

Monsieur Pierre GLAUDES  
Directeur de la section des unités de recherche  
Agence d'Évaluation de la Recherche et de  
l'Enseignement Supérieur  
20, rue Vivienne  
75002 PARIS

Monsieur le Directeur

Je vous adresse mes remerciements pour la qualité du rapport d'évaluation fourni à l'issue de la visite du comité d'expertise concernant l'unité « Ecosystème Intestinal, Probiotiques, Antibiotiques »

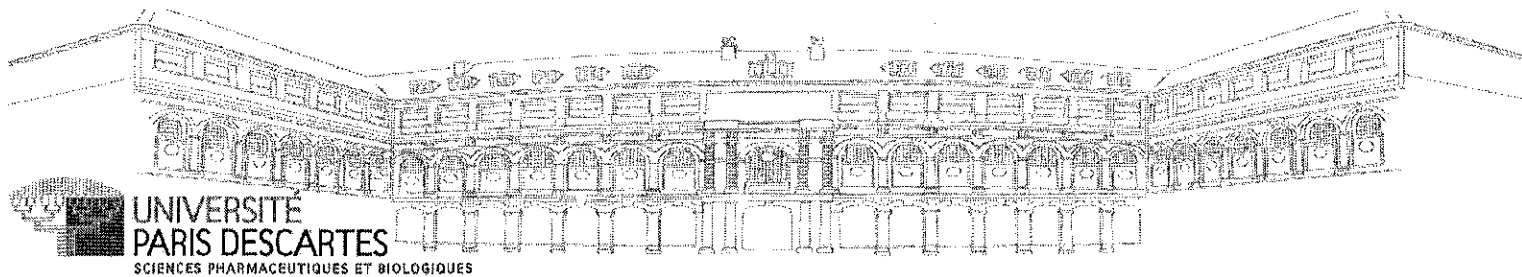
Vous trouverez ci-joint les réponses du Directeur de l'unité, Marie-José BUTEL, auxquelles le Président et moi-même n'avons aucune remarque particulière à rajouter.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de ma considération distinguée.

Le Vice Président du Conseil Scientifique



Stefano Marullo, DM, DesSci



Professeur Marie-José Butel  
Directeur du département Périnatalité-Microbiologie-Médicament  
Directeur de l'équipe « Ecosystème intestinal, probiotiques, antibiotiques » (EA 4065)  
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Paris, 22 mars 2013

To the expert committee members

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 advices. However, we have some clarifications to bring regarding their comments.

1- Assessment of the unit.

Concerning members from Conservatoire National des Arts et métiers (CNAM), if one member (professor) has already joined our team, it is under discussion with the scientific council of CNAM for the two other people (i.e., a research engineer and an assistant-engineer).

2- Weaknesses and threat.

The expert panel needed to clarify our relationships with the team at INRA which bring us the access to high throughput sequencing techniques for studying the gut microbiota. In particular, the experts raise the question of the unit that will take the lead concerning publications originating from this collaboration. We are the coordinator of the projects. It is our team which designed them, which is responsible for samples collections, for relationships with the clinical units and other research teams (e.g. epidemiologists for the follow-up of the cohorts) and which have the expertise concerning the gut microbiota in neonates. For all these reasons, our team will be the lead of publications. We chose to collaborate with this team for several reasons. First, this team has a well-known high expertise in these next generation sequencing approaches. Second, we do not have at this time such platform in our university. Third, the researcher we plan to recruit in 2013 has already collaborated with this team.

A handwritten signature in black ink, appearing to read "MJ Butel", is written over a light blue circular stamp.

Marie-José BUTEL