BAPS - Bactéries pathogènes et santé

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Écosystème microbien digestif et Santé

EMDS

Under the supervision of the following institutions and research bodies:

University Paris-Sud

January 2014

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

Department for the evaluation of research units

On behalf of AERES, pursuant to the Decree of 3 november 2006[1]*,*

- Mr. Didier HOUSSIN, president
- Mr. Pierre Glaudes, head of the evaluation of research units department

On behalf of the expert committee,

- Mr Michel POPOFF, chair of the committee

[1] The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n ° 2006-1334 of 3 November 2006, as amended).

Evaluation report

This report is the result of the evaluation by the experts committee,the composition of which is specified below.

The assessments contained herein are the expression of an independent and collegial deliberation of the committee.

Unit name:	Écosystème microbien digestif et Santé
Unit acronym:	EMDS
Label requested:	EA
Present no.:	EA4043
Name of Director (2013-2014):	Ms Anne COLLIGNON
Name of Project Leader (2015-2019):	Ms Claire JANOIR

Expert committee members

Chair:	Mr Michel POPOFF, Pasteur Institute, Paris
Experts:	Mr Michel ARTHUR, University Pierre et Marie Curie, Paris
	Ms Paola MASTRANTONIO, Istituto Superiore di Sanita, Rome, Italy
	Ms Guylène PAGE, University of Poitiers (CNU representative)

Scientific delegate representing the AERES:

Ms Sophie DE BENTZMANN

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

MrJean-Jacques GIRERD, University Paris-Sud

Mr Marc PALLARDY (Representative ED n°425)

1• Introduction

History and geographical location of the unit

The unit is located in the Chatenay-Malabry Pharmacy campus, Faculty of Pharmacy, University Paris-Sud. The EA 4043 exists since 1993 with various projects on the study of the microbial digestive ecosystem, and with INRA contract (MICALIS unit).

Management team

Ms Anne COLLIGNON (PU PH), was the head of the unit "Ecosystème microbien digestif et Santé" since 2001 and is responsible for the first axis of research "*Clostridium difficile* and its interactions with the host and the microbial digestive ecosystem" and will retire during the next contract. Ms Claire JANOIR, who is a member of the team since 1999, is applying as the next Director for the new contract (2015-2019) and will take the lead of the first axis of research. A PI (PU PH) will be responsible for the second axis of research "Antibiotic resistance in staphylococci".

AERES nomenclature

SVE1 Biology, health

SVE1_LS6 Immunology, microbiology, virology, parasitology

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	10	11
N2: Permanent researchers from Institutions and similar positions		
N3: Other permanent staff (without research duties)		
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	2
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**11**	**13**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	7	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	6	4

2 • Overall assessment of the interdisciplinary unit

The team is a nationally and internationally well recognized research group in the study of Clostridium difficile infection and in the antibiotic resistance in clostridia. The research projects concern a medically important field, since C. difficile is the most frequent cause of nosocomial diarrhea worldwide and was responsible for recent severe outbreaks. The team is in particular well known for the investigation of C. difficile surface components and intestinal colonization by this pathogen based on gnotoxenic animal models and analysis of microbiota. The team has multiple national and international collaborations, and it is competitive and attractive for recruiting professors, assistant-professors and PhD students as well as for obtaining financial funding.

- **Strengths and opportunities related to the context**

- the team has a long standing and unique expertise in the study of the interactions of C. difficile with microbial digestive eco-system, including the use of gnotobiotic animals.

- the team has a long experience and competence in the investigation of C. difficile surface components and characterization of transposons and antimicrobial resistance in Clostridia.

- in its current organization, this is a multidisciplinary team with 6 HDR (4 HDR + 2 équivalents, Doctorats d'État en Sciences Pharmaceutiques) and 3 additional supervisors (bacteriologists, microbiological clinicians, molecular and cellular biologists, biochemists) with a strong expertise in gnotobiotic animal models.

- the rapidly evolving knowledge based on the intestinal flora, in particular due to advances in DNA sequencing techniques, should provide interesting opportunities for collaboration in the near future, in particular in the framework of existing collaborations with INRA.

- the attractiveness of the team for hiring and promoting assistant professors and professors is effective since, during the last 5 year contract, 1 professor (PU-PH) 1 assistant professor (MCU) and 2 assistant hospitalo-universitaires (AHU) were recruited.

- the team has collaborations with multiple national and international partners, notably the Center for Molecular Microbiology, (Imperial College London, UK), the Institute of Infection, Immunity, and Inflammation (University of Nottingham, UK), the Instituto of Technologia Quimica e Biologica (Universida de Nova de Lisboa, Portugal), the Veterinary Science and Microbiology team, (University of Arizona, USA); the INRA group under contract (Unit MICALIS), the Laboratory "Pathogénèse des bactéries anaérobies", (Institut Pasteur, Paris), the team "Ecosystème intestinal, probiotiques, antibiotiques" (Université Paris Descartes, Paris) and also with local teams, technical platforms, Institut Galien (UMR CNRS 8612) for the development of the mucosal vaccination against C. difficile infections and with EA401 "Matériaux et Santé" for chemical analysis of polysaccharides.

- a significant number (10 in total) of PhD students have been or are currently formed.

- the team has easy access to facilities and technical resources, such as the axenic animal care facilities of EA 4043 and the “Institut Fédératif de Recherche - Institut Paris-Sud Innovation Thérapeutique” (“IFR-IPSIT”), technical platforms at the Faculty, the L2 laboratory of the INSERM unit UMR-S 984, close to their unit, for the cellular microbiology studies.

- the team has been quite successful for fund raising fropm various sources such as Ministry funds, 2 grants from ANR, one European grant (FP7 HEALTH-2007-B-223585 HYPERDIF, 2008-2010) and 5 industrial projectS.

- **Weaknesses and threats related to the context**

- all members of the team have important teaching and hospital duties, including the future team leader for the next contract.

- the committee found that there is a relatively large number of research axes in a very competitive area, in particular for the S. aureus project.

- the field of C. difficile is highly competitive at international level.

- there are no post-doctoral fellows and a limited number of projects financed by external funds can be used for postdoctoral fellows.

- moving to "Plateau de Saclay" in the framework of the UPSay operation, scheduled for 2017-2018, constitutes an opportunity but also a threat particularly regarding the distance to hospitals that may result in great disturbances in the research activities.

- **Recommendations**

- the leader and the senior scientists should carefully identify the research projects that will allow the team to be competitive and to improve the impact of their publications.

- the team should concentrate the efforts to participate in EU-funded consortiums (Horizon 2020, Marie Curie etc,.), and in Joint ventures with pharmaceutical companies. Many current activities both on S. aureus and C. difficile focus on mechanisms of resistance to antibiotics or mucosal vaccine development. Thus, the topics should be very attractive for raising external funds recruiting post doctoral fellows.

3 • Detailed assessments

Assessment of scientific quality and outputs

The level of publications was found to be very good. 29 publications are directly related to the research projects of the team during the previous 5 year contract and mostly with IF ranking between 3 and 5 that correspond to the best journals of the C. difficile discipline and 3 with IF comprised between 5 and 10. Among the 29 publications, 23 have scientists of the team act as main authors (first and/or last position).The publications cover the two axes of research of the team including C. difficile colonization and C. difficile surface components, as well as antibiotic resistance in Clostridia. Two publications are breakthroughs in the knowledge of C. difficile and intestinal ecology, and microbiota investigation in newborns in relation with the risk of colonization by C. difficile. In addition, the team has participated to 51 publications in collaboration with other teams and to 9 book chapters.

Assessment of the unit's academic reputation and appeal

The academic reputation of the team is considered excellent based on its international notoriety. Indeed, the team is an internationally recognized leadership on specific topics like C. difficile surface components, microbial ecology of the gastrointestinal tract and risk factors of C. difficile colonization as illustrated by 11 invited conferences in the domain and 39 oral or poster presentations in national and international meetings.

The team is attractive for Master and PhD students (14 Master 2 and 10 PhD students during the 2009-2013 period including 4 foreigner students). However, no post-doctoral fellow has been recruited during the period. One student received a thesis award 2009. The team has excellent and fruitful collaborations at national and international levels. The team succeeded in obtaining two ANR grants, one as coordinator and one as partner, as well as an EU FP7 project as partner, and 4 industrial grants including 4 as coordinator. Members of the team participated to scientific committees of 3 international meetings and have organized 3 national meetings. Members of the team have been invited to give conferences in national, European, and international meetings (22 in total). It is noteworthy that the team provided its expertise in C. difficile animal models to several national and international teams.

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

The team obtained 3 academic and 4 industrial grants including participation to clinical research projects (Non-interventional biomedical research ICD-MATER (2011-2012), Clinical multicentric research project SERODIFF (2013-2015), Biomedical multicentric research project PORTADIFF (2013-2014), Clinical multicentric research project Microbs (2012-2013), 1 international epidemiological group (EUCLID, European study group Clostridium difficile of European Society of Clinical Microbiology and Infectious Diseases). The team participated to clinical networks (members of the team participate to the national antibiotic resistance committee, a member of the team presides a clinical research group "Groupe de Microbiologie Clinique", and another member is part of the "Conseil d'administration de l'association OutcomeRea reseau microbiologique associé" and member of the "College de Bactériologie Virologie des Hopitaux Généraux"). However, no patent has been submitted.

Assesment of the unit's organisation and life

The organization of the team is well structured. Each project is driven by a researcher in charge and participants including PhD students and collaborators are well identified. The Assistant Professors share different responsibilities such as the laboratory meeting organization and website management (http://www.emds.u-psud.fr/), Animal care facilities (authorization, N°A9201991), Hygiene and security.

The team is dynamic with an excellent communication between all the members. The quality and friendly communication with the supervisors were appreciated by all students. Weekly laboratory meetings and regular scientific meetings with other teams from the University reinforce the interactions between all the members of the team and with other scientists in the campus. A weekly laboratory meeting concerning technical difficulties, planned experiments and bibliography is organized. A monthly meeting is organized regarding strategy for research and publication. The PhD and Master students as well as Assistant Professors present their work and participate actively to the general discussion. A monthly meeting of the IPSIT (Institut Paris-Sud Innovation Thérapeutique) is scheduled with external invited speakers that allow to broaden the formation of young researchers through a multidisciplinary approach (a team member is part of the organization board of the IPSIT scientific meetings).

Additionally,participation, according to the subject, to the MICALIS scientific meetings is effective at the INRA in Jouy en Josas. Permanent staff, PhD and Master students actively participate to national and international scientific meetings to present their work and discuss with other colleagues. There is a permanent formation policy including continuous training of technical staff and researchers. The management is well organized with responsibility shared between all the professors and assistant professors.

Assessment of the unit's involvement in training through research

Numerous PhD and Master students have been supervised by the team (7 PhD during the last period, 3 in progress, 14 Master 2 students). Two former PhD students are currently in post-doctoral fellow training at Pasteur Institute (Paris) and University of Sherbrooke (Canada). Two other former PhD students have been recruited as Assistant Professors (in the team unit after a 3 year-post-doctoral training and at the “Université Paris Descartes”). One former PhD student has been recruited as microbiologist in the industry. Three PhD students are currently working in the unit. Furthermore, 2 AHU will be recruited in November 2013, and will be registered as PhD student. Members of the team are involved in the management of Master "Médicaments et autres produits de santé". The team leader is responsible for the Microbiology pole including Master 1 and Master 2. Additionally, team members are deeply involved in Master 1 or Master 2 trainings as exemplified by the facts that: a) at the M1 level, the team leader is responsible for the Master1 module "Interactions hôtes-microorganismes" UE95B, b) a team leader is responsible for the module "Exploitation des genomes pour le diagnostic et le traitement des maladies infectieuses" EU95C, c) a team professor is responsible for the Master 1 module "Microbiologie Générale" ,d) at the M2 level, the team leader is responsible for the course UE1 (UE, Unité d'enseignement) "Mécanismes cellulaires et moléculaires de la pathogénie de microorganismes", e) a team professor is responsible for the course UE2 "Antiinfectieux, mécanismes d'action et résistance des microorganismes".

The team belongs to the doctoral school "Innovation thérapeutique: du fondamental à l'appliqué" ED425, and the team leader is responsible for the Microbiology pole and for the corresponding PhD students. A team professor is responsible for the international relation and student exchange in the framework Erasmus project. 3 team members are in progress for HDR. It is noteworthy that supervision of PhD and Master students is well equilibrated between all the professors and assistant professors of the team. The research projects of the team, C. difficile infection and development of vaccine as well as antibio-resistance, are in the scope of the Doctoral School facilitating the recruitment of PhD students by the team.

Assessment of the strategy and the five-year plan

The EA 4043 unit will undergo major restructuration, during the next five-year contract. The team will have a new leader. In addition, this new team will join UPSay and since the INRA group from Jouy en Josas will also become a member of UPSay, it has been decided that the contract with INRA would not be renewed. Nonetheless, the collaborations with the INRA Partners belonging to the TGU MICALIS will continue. The five year plan is based on two distinct axes of research: (i) C. difficile pathogenesis including 4 sub-axes (immune response to surface proteins, characterization of surface proteins involved in colonization, mucosal vaccine strategy, and biofilm formation), and (ii) antibiotic resistance in Staphylococcus aureus and other Gram-positive bacteria.

The first axis “C. difficile and its interaction with the host” is mostly a continuation of previous research activities and will be coordinated by the new team leader. The first specific objective is to decipher the role of several surface components of C. difficile vegetative cells and spores in colonization. These components include “Clostridial wall proteins“, peptidoglycan, "Moonlighting" proteins, and spore proteins. The second specific objective is to characterize the innate and immune response to these bacterial surface components. This will involve use of cellular and animal models as well as analysis of human samples. The third objective is to develop a mucosal vaccine strategy based on identification of protective antigen combinations in animal models. They also propose to develop vectorization strategies and passive immunization. The fourth objective is to evaluate the role of biofilm in bacterial-host interactions based on in vitro and animal studies. Together, these objectives form an ambitious and coherent research project. Drawbacks include the very large number of surface structures and questions that will be addressed by members of the team. It seems that the project is excellent in identifying relevant research areas to further elucidate understanding of the basis for C. difficile colonization and infection. However, several aspects do not appear to be based on hypotheses and the number of objectives appears rather important with respect to the number of manpower that will be devoted to each of these objectives.

The second axis will concern the mechanism of resistance to antibiotics acting on translation in staphylococci. This axis will be coordinated by a professor, who has been recently recruited by the team. A first specific objective is to analyze the genetic environment of cfr gene in clinical isolates. This gene encodes a ribosomal RNA methyltransferase conferring resistance to linezolid, streptogramins A, lincomycin and pleuromutilin antibiotics. Transfer of cfr gene to various bacterial species will be tested in vitro and in gnotobiotic mice. A second objective concerns the characterization of a new mechanism of resistance to mupirocin, a leucyl-tRNA synthetase inhibitor, which has been identified by the investigator in coagulase negative staphylococci. This will be based on whole genome sequencing but the rationale for using this technique has not been provided. As a third objective, it is mentioned that analyses will be performed to establish correlations between virulence factors and colonization fitness in S. aureus. These specific objectives are interesting but the long term strategy and the relationships with the first research axis are not sufficiently described.

The two axes of research will benefit from the animal models developed in the previous contract. All the axes and sub-axes of research are pertinent and promising at the fundamental level with perspectives of translation to the medical level. However, priorities should be defined among the numerous research sub-axes, in adequacy with the limited human resources of the team. It is essential to identify the most promising projects for future successes in competitive funding, attractiveness for post-doctoral fellows, and design of successful strategies for publications in higher ranked journals.

4 • Theme-by-theme analysis

Theme 1: Clostridium difficile and its interactions with the host and the microbial digestive ecosystem

Manager's name: Ms Anne COLLIGNON and Ms Claire JANOIR

Workforce

Theme workforce in Full Time Equivalents	As at 30/06/2013	As at 01/01/2015
FTE for permanent professors	2,5	4,25
FTE for permanent EPST or EPIC researchers		
FTE of other permanent staff without research duties (IR, IE, PRAG, etc.)		
FTE for other professors (PREM, ECC, etc.)	0,5	0,25
FTE for postdoctoral students having spent at least 12 months in the unit		
FTE for other EPST or EPIC researchers (DREM, etc.) excluding postdoctoral students		
FTE for other contractual staff without research duties		
FTE for doctoral students	2	
TOTAL	**5**	**4,5**

Detailed assessments

Three different axes have been conducted during the last five year period, which involved colonization factors, analysis of interactions with intestinal microbiota and development of a vaccinal strategy. Regarding the first axis, among the main results that should be mentioned are: a) the role of Cwp84 in the pathogenic process of C. difficile, b) the fact that colonization factors are regulated by environmental conditions (hyperosmolarity, iron depletion and sub-inhibitory concentrations of antibiotics) demonstrated using in vitro transcriptomic studies, c) the obtention of surface proteins mutants in C. difficile, thanks to the development of ClosTron by the team of Nottingham (European contract FP7-HEALTH-2007-B-223585 HYPERDIFF), their study to ascertain their functions, the in vivo transcriptomic studies in their monoxenic mouse model on the 630 strain (first sequenced strain) and the epidemic hypervirulent strain 027 R20291 in collaboration with the Laboratory of Pathogenesis of anaerobic bacteria "Institut Pasteur". The second axis was focussed on the study of the intestinal microbiota of young infants according to C. difficile colonization (Press release by the American Society for Microbiology). Results show that the presence of C. difficile was associated with changes in the ecosystem's composition, especially with absence of bifidobacteria and that toxigenic strains responsible for adult infections circulate in healthy infants who represent a potential reservoir of infectious bacteria. The third axis provided evidence that mucosal immunization with surface proteins could at least partially inhibit colonization by C. difficile and protect the hamster against C. difficile infection.

Overall opinion of the theme

The theme of C. difficile colonization is of great importance since C. difficile infections are the most frequent cause of nosocomial diarrhea and colitis worldwide and are one of the main side effects of antibiotherapy. A better understanding of (i) the development of C. difficile in the intestinal tract, (ii) the role of microbiota, and (iii) the perturbation of the microbiota by antibiotics is critical to develop efficient prevention strategies of C. difficile infections and for a better adaptation to antibiotic treatment. The axes investigated by the team which are C. difficile factors involved in intestinal colonization, sequences of C. difficile colonization in the intestinal tract, influence of the microbiota are pertinent and crucial for a better knowledge of C. difficile infections. Relevant results have been obtained by the team during the previous period as illustrated by the publications, invited conferences, attractiveness for PhD students, obtention of academic and industrial grants.

- **Strengths and opportunities:**

The team is pionner in the investigation of C. difficile surface components and has obtained original results in the analysis of the intestinal colonization by C. difficile (two publications are breakthroughs in this domain). A main part of the originality of this research axis is based on the team expertise in gnotoxenic animal models. The team has national and international collaborations sharing their expertise in animal models and has benefited from the experience of external teams in bacterial genetics. In addition, investigations in the human host in natural conditions are performed through clinical research projects. This research axis has important translational potential in the medical field regarding the development of vaccine.

- **Weakness and threats:**

- the C. difficile axis is increasingly competitive.

- there is absence of team members involved in full time research.

- no post doctoral fellow support is currently supporting the competiveness of this research axis.

- **Recommendations:**

- the leader and the senior scientists should carefully identify the research subaxes that will allow the team to be competitive and to improve the impact of their publications.

- the team would concentrate the efforts to participate to external grants allowing the recruitment of post doctoral fellows.

- the most pertinent research axis concerns the innate and adaptive immune host responses to C. difficile, which will allow to better understand the factors involved in the colonization of the digestive tract by this pathogen. The team has already characterized cell surface components which are the most appropriate candidates to elicit the immune response, and has the experience in animal models to investigate the intestinal colonization by C. difficile. This part would be reinforced including the participation and/or collaboration of cellular biologists and immunologists.

Theme 2:

Antibiotic resistance gene transfer in the microbial digestive ecosystem: role of clostridial conjugative transposons

Manager's name:

Mr Thierry LAMBERT (until 2015)

After January 2015, modification of theme n°2 : "Antibiotic resistance andvirulence in Staphylococci"
Manager : Ms Florence DOUCET-POPULAIRE

Workforce

Theme workforce in Full Time Equivalents	As at 30/06/2013	As at 01/01/2015
FTE for permanent professors	1,5	0,5
FTE for permanent EPST or EPIC researchers		
FTE of other permanent staff without research duties (IR, IE, PRAG, etc.)		
FTE for other professors (PREM, ECC, etc.)		0,25
FTE for postdoctoral students having spent at least 12 months in the unit		
FTE for other EPST or EPIC researchers (DREM, etc.) excluding postdoctoral students		
FTE for other contractual staff without research duties		
FTE for doctoral students		
TOTAL	**1,5**	**0,75**

Detailed assessments

Overall opinion of the theme

Antibiotic resistance is a major problem in the control of infectious diseases. Antibiotic resistance is more prevalent in some groups of pathogens like S. aureus. Clostridia which are inhabitants of the digestive tract represent a reservoir of resistance genes. Genetic transfer of antibiotic resistance determinants is a crucial mechanism in theevolution of emergent pathogens.

Relevant results have been obtained in the axis of antibiotic resistance in clostridia and genetic analysis of transfer by conjugative transposons. The new second axis on investigation of new mechanisms of resistance, horizontal transfer of resistance, and correlation between virulence factors and colonization is promising. Of note, antibiotic resistance to two antibiotics acting on protein synthesis, linezolid and mupirocin, will be investigated in gram positive bacteria (Staphylococcus aureus).

- **Strengths and opportunities:**

The team has the experience and competency in genetic analysis of antibiotic resistance. The gnotoxenic animal model is a valuable tool to analyze gene transfer in the intestinal tract in vivo and to investigate the virulence factors. The development of studies of axis 2 will benefit animal models developed by EA 4043. The involvement of team members in clinical activities or responsibilities is an excellent opportunity for investigation of variant clinical isolates and translation of research projects to medical application.

The work is also part of a translational approach with funding already obtained MICROBS (multicentric study). The sequencing of the genome of S. aureus strains having a specific antibiotic resistance profile will bring a new technical expertise in genomics and bioinformatics within the team.

- **Weaknesses and threats:**

The S. aureus research field is competitive.
Axis 2 shows no link with the first axis as resistance mechanisms studied will be specific to S. aureus.
There is an absence of team members involved in full time research as well as no post doctoral fellow on this axis.

- **Recommendations:**

A better definition of the specific aims of the project regarding the virulence factors of S. aureus and a better interaction between the two research axes of the team are recommended.

5 • Conduct of the visit

Start :	January 13th, 2014 at 9.00 am
End :	January 13th, 2014 at 6.00 pm

Visit site :	EA 4043
Institution :	Faculty of pharmacy, University Paris-Sud
Address :	Av JB Clement, Chatenay Malabry

Conduct or programme of visit:

9h-9h15	Presentation of AERES visit philosophy and of expert committee by the AERES scientific delegate
9h15-10h15	Presentation of the unit, past activities
10h15-11h00	Presentation of the unit, projects
11h00-11h15	Break
11h15-11h45	Meeting with technical staffs, non-permanents and permanent researchers
11h50-12h10	Meeting with the director
12h10-12h30	Meeting with the supervising institutions and bodies
12h30-13h45	Lunch
13h45-16h45	Closed meeting of the committee
17h00	End of the visit

6 • Supervising bodies' general comments

UNIVERSITÉ PARIS SUD

Comprendre le monde,
construire l'avenir®

Le Président de l'Université Paris-Sud

à

Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
AERES
20, rue Vivienne
75002 Paris

Orsay, le 4 avril 2014

N/Réf. : 85/14/JB/LM/AL

Objet : Rapport d'évaluation d'unité de recherche
N° S2PUR150007654

Monsieur le Directeur,

Vous m'avez transmis le 13 mars dernier, le rapport d'évaluation de l'unité de recherche Bactéries pathogènes et santé - n° S2PUR150007654 et je vous en remercie.

L'université se réjouit de l'appréciation portée par le Comité sur cette unité et prend bonne note de ses suggestions. Elle suivra avec attention la mise en place de la nouvelle structure de l'unité.

Vous trouverez en annexe les éléments de réponse de Mesdames Anne COLIGNON, directrice actuelle de l'unité et Claire JANOIR, candidate à la direction de l'unité de recherche.

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

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Châtenay-Malabry, March 25, 2014

English version
Our Response to the AERES Expert Committee Report

The entire team thanks the AERES Committee of Experts for their work and the constructive remarks outlined in their evaluation report.
We very much appreciate the recognition of our expertise, our national and international recognition and our attractivity.
We are aware of some weaknesses, especially the absence of fulltime researchers and post-doctoral fellows. Consequently, one of our first objectives in the future contract will be to find funding in order to recruit one or two post-doctoral fellows. The ongoing proposals are already written in that direction.

Regarding our strategy for the future contract, we will take into account the Committee's recommendations. However, we would like to clarify some points concerning the suggestions which have been made to concentrate our forces on a few sub-axes of axis 1, and the necessity to reinforce the links between the two axes.
During the next contract, the themes of the unit will be centered on two axes concerning two key nosocomial pathogens: *Clostridium difficile* and Staphylococci. These fields are highly competitive, however, their medical importance can favor obtaining funding based on institutional and industrial calls. In addition, the two axes projects are linked to the skills and the expertise of the team members.

The first axis entitled, "*Clostridium difficile* pathogenesis: role of surface components " has been one of our unit's major project and one which has gained our unit international recognition. We will continue studying the colonization process of the digestive tract with: 1) a fundamental sub-axis regarding surface proteins and their role in colonization and biofilm formation; and 2) a translational sub-axis regarding the host immune response against these proteins (study in animal models and in human clinical trials) as well as pursue the development of the vaccinal strategy by mucosal route in animal models.
The Committee has recommended that we should concentrate our efforts on the study of the immune response and the development of vaccinal strategy, since these topics are attractive for raising industrial funding (some of our projects have already received industrial funding). We are fully aware of the possibilities of the valorisation of these studies, however, we think that it is also crucial to continue to develop more fundamental research and to characterize new surface antigens involved

in colonization in order to improve the efficiency of our mucosal vaccine strategy by combining several vaccine antigens. Several surface components have already been identified and have been presented in our project, whereas only the more promising will be further characterized.
To avoid dispersion and according to technological evolution, the thematic intestinal microbiota analysis will be stopped but occasional collaborations with INRA teams (belonging to future University Paris Saclay) will be done to answer specific questions.

The second axis entitled, "Antibiotic resistance in Staphylococci" is going to be developed by a professor with hospital functions (PU-PH) recruited during the ongoing contract. This axis is in adequation with her expertise and her hospital functions. The project, which will be developed and have priority, concerns antibiotic resistance targeting the ribosome in staphylococci. As presented during the oral presentation of our project, one of the resistance mechanisms to linezolid is shared between clostridia and staphylococci. Studies on these bacteria will be performed in parallel, thus promoting the development of technical and thematic interactions between the unit's two research axes. In addition, in vivo transfer studies will be performed in gnotobiotic animal models using the expertise of the team members.

Finally, all the members of the unit with hospital functions will participate to clinical studies concerning the two axes, *C. difficile* and staphylococci.

Version française
Objet : Réponse au rapport du Comité d'experts de l'AERES

Toute l'équipe remercie le comité d'experts pour son évaluation de l'unité EA4043 et pour les remarques constructives formulées dans le rapport concernant le projet de recherche pour le contrat quinquennal 2015-2019.
Nous apprécions la reconnaissance par le comité d'une part, des expertises de l'unité et, d'autre part, de sa notoriété nationale et internationale. Nous sommes conscients de certaines faiblesses, en particulier l'absence de chercheurs temps plein et de post-doctorants. Aussi, l'un des objectifs du prochain contrat quinquennal est de réussir à trouver des financements pour l'accueil d'au moins un à deux post-doctorants. Les projets en cours sont d'ores et déjà rédigés en ce sens.
Concernant la stratégie pour le contrat à venir, nous tiendrons compte des recommandations du comité. Nous souhaitons cependant apporter quelques précisions concernant la suggestion de concentrer les forces de l'équipe sur quelques thématiques de l'axe 1, et le renforcement nécessaire des liens entre les deux axes de recherche développés dans les prochaines années.

L'unité existante est organisée autour de deux axes, et cette organisation sera similaire dans le prochain quinquennal, bien que les thématiques évoluent. Les thématiques seront centrées sur deux pathogènes nosocomiaux de grande importance, *Clostridium difficile* et les staphylocoques. La recherche sur ces bactéries est certes très compétitive, mais leur importance médicale favorise l'obtention de financements sur projets institutionnels et industriels. D'autre part, les projets de recherche des deux axes sont fondés sur les compétences et expertises des membres de l'équipe.

Le premier Axe intitulé "Physiopathologie des infections à *Clostridium difficile* : rôle des composants de surface" est la suite d'un de nos axe de recherche développé dans le laboratoire depuis plusieurs années pour lequel nous sommes reconnus. Nous poursuivrons l'étude du

processus de colonisation du tube digestif avec : 1) un volet fondamental sur l'étude des protéines de surface et leur rôle dans la colonisation et la formation d'un biofilm ; et 2) un volet translationnel comportant l'étude de la réponse de l'hôte vis à vis de ces protéines (étude en modèle animal et chez l'homme par des essais cliniques) et la poursuite du développement d'une stratégie vaccinale par voie muqueuse en modèle animal. Compte-tenu de la taille de l'équipe, le comité suggère de nous focaliser sur l'étude de la réponse immunitaire et le développement de la stratégie vaccinale, soulignant que ces thématiques sont favorables à l'obtention de contrats industriels (certains projets bénéficiant déjà d'un financement industriel). Nous sommes effectivement conscients de la valorisation possible à moyen terme de ces études mais il nous semble aussi important de continuer à développer en amont une recherche plus fondamentale pour caractériser de nouveaux antigènes de surface jouant un rôle dans la colonisation afin d'améliorer l'efficacité de notre stratégie vaccinale en combinant plusieurs antigènes d'intérêt. Plusieurs composants de surface ont été identifiés et présentés dans le projet de l'unité, mais le travail de caractérisation ne sera poursuivi que sur les plus intéressants d'entre eux dans la perspective de la stratégie vaccinale.
Par ailleurs, pour éviter de diversifier trop nos axes de recherche, et compte-tenu des évolutions technologiques, la thématique sur l'analyse du microbiote intestinal ne sera pas reconduite. Cependant des collaborations avec des équipes INRA (qui seront membres de la future Université Paris Saclay) seront maintenues sur des projets précis et permettront, en fonction de l'évolution des travaux, de répondre à des questions ponctuelles.

Le deuxième axe intitulé "Résistance aux antibiotiques chez les Staphylocoques" va être développée par un PU-PH recruté au cours du contrat actuel. Cette thématique est en adéquation avec son expertise et ses fonctions hospitalières. Le projet de cet axe qui sera développé en priorité concerne la résistance aux antibiotiques ciblant le ribosome chez les staphylocoques. Comme exposé lors de la présentation orale du projet, un des mécanismes de résistance au linézolide est commun chez les staphylocoques et les clostridies et des études seront menées en parallèle dans les deux genres, favorisant ainsi le développement de liens techniques et thématiques entre les deux axes. Par ailleurs, l'expertise de l'équipe dans les modèles animaux gnotoxéniques sera valorisée par les études *in vivo* de transfert génétique.

Enfin, tous les membres hospitalo-universitaires de l'équipe seront impliqués dans les études cliniques développées sur les deux thématiques, *C. difficile* et les staphylocoques.

Professeur Anne COLLIGNON Professeur Claire JANOIR