M2iSH - Microbes, intestin, inflammation et susceptibilité de l'hôte

Rapport Hcéres

HCERES

High Council for the Evaluation of Research and Higher Education

Research units

HCERES report on research unit:

Microbes, Intestine, Inflammation and Susceptibility of the Host

M2iSH

Under the supervision of the following institutions and research bodies:

Université d'Auvergne - UDA

Centre Hospitalier Universitaire de Clermont-Ferrand – CHU Clermont

Institut National de la santé et de la Recherche Médicale - INSERM

Institut National de la recherche Agronomique - INRA

Evaluation Campaign 2015-2016 (Group B)

HCERES

High Council for the Evaluation of Research and Higher Education

Research units

In the name of HCERES,[1]

Michel COSNARD, president

In the name of the experts committee,[2]

Alain FILLOUX, chairman of the committee

Under the decree No.2014-1365 dated 14 november 2014,

[1] The president of HCERES "countersigns the evaluation reports set up by the experts committees and signed by their chairman." (Article 8, paragraph 5)

[2] The evaluation reports "are signed by the chairman of the expert committee". (Article 11, paragraph 2)

Evaluation report

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

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

Unit name:	Microbes, Intestine, Inflammation and Susceptibility of the Host
Unit acronym:	M2iSH
Label requested:	INSERM
Current number:	1071
Name of Director (2015-2016):	Mr Nicolas BARNICH
Name of Project Leader (2017-2021):	Mr Nicolas BARNICH

Expert committee members

Chair:	Mr Alain FILLOUX, Imperial College London, UK
Experts:	Mr Alain CHARBIT, INSERM, CNRS, Faculté de Médecine Paris Descartes, (Representative of the INSERM-CSS)
	Mr Nicolas LAPAQUE, INRA, MICALIS

Scientific delegate representing the HCERES:

Mr Kamel BENLAGHA

Representatives of supervising institutions and bodies:

Mr Philippe DULBBECO, Université d'Auvergne

Mr Alain ESCHALIER, Université d'Auvergne

Ms Emmanuelle MAGUIN, MICA, INRA

Ms Stéphanie POMMIER, INSERM

Mr André SALAGNAC, CHU Clermont-Ferrand

Head of Doctoral School:

Mr Jean-Marc LOBACCARO, ED n°65 « Santé Agronomie et Environnement »

1 • Introduction

History and geographical location of the unit

The creation of the unit was initiated by Ms Arlette DARFEUILLE-MICHAUD in 2008 in the form of a Young INRA team with the JE2526 label (USC-2018, since 2005). Following the AERES evaluation in February 2011, the unit was transformed in 2012 into the UMR U1071 under the authority of INSERM and Université d'Auvergne. The unit name was then coined as M2iSH for "Microbe, Intestine, Inflammation and Host Susceptibility". The death of Ms DARFEUILLE-MICHAUD in 2014 resulted in the installation of the current director, Mr Nicolas BARNICH. In its current form, the unit mostly includes teaching staff from the Université d'Auvergne and physicians from the CHU Clermont-Ferrand, with only one full time researcher appointed by INSERM. The unit is made of one single team and is based on the campus of the Faculté de Médecine et de Pharmacie (Place Henri-Dunant, Clermont-Ferrand) where it occupies about 600 m^2 on a single floor.

Management team

The management team includes the director (Mr Nicolas BARNICH) and a deputy director (Mr Richard BONNET). The director can consult the laboratory council, which includes representatives of all personnel categories and meets every month.

HCERES nomenclature

SVE1_LS6,

SVE1_LS4,

SVE1_LS7

Scientific domains

The unit has historically founded its activity and visibility by studying the impact of enteric bacteria, first on chronic inflammatory bowel diseases (Crohn's disease) and now on colorectal cancer. The expertise of the unit encompasses a variety of techniques from basic molecular microbiology, cellular biology and immunology up to *in vivo* models and physiopathology of the disease, with strong expertise in gastroenterology and oncology and involving the clinicians.

Unit workforce

Unit workforce	Number on 30/06/2015	Number on 01/01/2017
N1: Permanent professors and similar positions	13	15
N2: Permanent researchers from Institutions and similar positions	1	1
N3: Other permanent staff (technicians and administrative personnel)	6	8
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	2	
N6: Other contractual staff (technicians and administrative personnel)	5	
N7: PhD students	11	
TOTAL N1 to N7	**38**	
Qualified research supervisors (HDR) or similar positions	11	

Unit record	From 01/01/2010 to 30/06/2015
PhD theses defended	13
Postdoctoral scientists having spent at least 12 months in the unit	11
Number of Research Supervisor Qualifications (HDR) obtained during the period	4

2 • Overall assessment of the unit

Introduction

The unit UMR U1071 INSERM/Université d'Auvergne, or M2iSH, is interested in the evolution and the pathoadaptive development of bacteria within a host. In particular it studies pathogens involved in the etiology of acute and chronic inflammatory bowel diseases (IBD) and, more recently, of colorectal cancer. This unit gained an international recognition when it conducted a seminal work and first discovered the abnormal colonization of the ileal mucosa of Crohn's Disease (CD) patients with a particular pathotype of *E. coli*, called adherent invasive *E. coli* or AIEC. This work was published in 1998, and since then a continuous and impressive series of publications has unravelled many aspects of this very peculiar host-pathogen interaction.

During the past previous years, the unit capitalized on this expertise and developed three majors themes: i) the molecular characterization of intestinal disease-associated *Escherichia coli*; this was more specifically in AIEC in CD, but similar approaches have been extended to *E. coli* strains associated with the progression of tumours in colorectal cancer (CRC), with emphasis on colibactin-producing *E. coli* strains; ii) the host-bacteria cross-talk at the intestinal mucosa site; in this theme, the unit deciphers the mechanisms of bacterial translocation through the

intestinal epithelium, the characterization of the bacterial and host factors associated with the process, and the overall impact of the colonization on the physiopathology; and iii) the development of innovative diagnostic tools and therapies, which makes use of very specific discoveries obtained in the unit such as the specific recognition of the CEACAM6 molecule by the bacterial adhesin FimH.

The future scientific strategy of the unit mostly pursues research work along these lines, which are promising and by far to be fully understood and exploited. This should lead to the development of improved diagnostic tools and therapeutic strategies. In brief, the research projects for the next five years will be focused on the interaction between pathogenic bacteria or pathobiont bacteria and the host, in the context of intestinal inflammation (Research Axis 1) or carcinogenesis (Research Axis 2) and the development of innovative diagnostic and/or therapeutic tools (Research Axis 3).

Global assessment of the unit

The evaluation committee recognized that this excellent to outstanding unit has acquired an international recognition in the study of the host-pathogen relationship associated with Crohn's disease. This covers a wide range of approaches that have unravelled detailed interactions between the *E. coli* strain AIEC and host receptors or other host susceptibility factors. What was initiated by the previous director has been not only continued with similar success but also with a continuous dynamic as suggested by the new project of the unit, although it is extremely ambitious. Several research lines have been built on previous preliminary data, and are ready to take off such as the importance of pathotypes in the progression of tumors in colorectal cancer, the role of exosomes in cell-cell communication and large omics approaches to identify new virulence determinants or host susceptibility factors. The committee considered that the integration between academics and clinicians is a tremendous success, which guarantees the project feasibility and the visibility of the unit. The niche which has been developed is quite unique and positioned the region of Clermont-Ferrand and the Université d'Auvergne at the forefront of international recognition in the domain of IBD and infection.

Strengths and opportunities in the context

By identifying a new pathotype of *E. coli* (AIEC) associated with Crohn's disease, the Unit has pioneered a field and is internationally recognized for it.

The unit comprises scientists and clinicians with multidisciplinary expertise, (microbiology, cell and molecular biology, immunology, gastroenterology, digestive surgery, internal medicine). The committee noticed that all the members interact extremely tightly and efficiently, demonstrating real synergy and willingness to work together.

The remarkable interface with local hospitals provides access to biological samples and allows the effective development of translational research projects. This is demonstrated by the ownership of 4 patents one of which was sold to a company with which the unit has a longstanding collaboration.

The unit is small and built around one single team but has an excellent publishing record.

The support/connection from/with the Université d'Auvergne is very strong and reflects the commitment of the unit members to teaching. This results in the ability of the unit to recruit excellent students

Despite a geographic location that might not be so well known outside French borders, the unit is very attractive from an international point of view. Several foreign post-docs have joined the unit (although none have left at the moment) and the unit was able to recruit a formal post-doc back from the States, which is currently the only full time researcher.

Weaknesses and threats in the context

There was a need to maintain the leadership of the unit in the field of AIEC bacteria and Crohn's disease after the death of Arlette DARFEUILLE-MICHAUD (2014) who was internationally recognized. This was a threat but the committee was clearly reassured that the new director had the scientific legitimacy and was unanimously supported by all unit members, and hopefully this will continue.

The unit has only one technical and administrative staff and only one full-time researcher. This is critical since at the same time the unit lost the only INRA researcher they had in the past and who left for personal convenience. This very limited support, combined with the important teaching activities of the team members, clearly restricts the intrinsic potential of the unit in research.

The team has decided to take high scientific risks on several new topics: impact of physical activity on microbiota composition in chronic diseases, role of exosomes in cell-cell communication, study of bacterial glycosylation on virulence modulation, development of animal models for chronic infection, translational and clinical studies… The committee feels that, even though all these directions are potentially original and promising, the project may look way too ambitious and the visibility of the unit might be lost or diluted if priorities are not clearly identified.

The financial support coming form companies is very high (25%) and the director indicated a possible risk of losing some of these current important financial partnerships that were tightly dependent on relationships established by the previous director. Yet the evaluation committee felt that there is no obvious reason for this to happen. Instead, attention should be given that major ANR or European project applications be posted in a timely manner in order to secure funding for the unit on the long term.

The director mentioned the need of a researcher specialized in bioinformatics (for omics approaches and the microbiota studies) as well as in glycobiology. The evaluation committee felt that these expertises should better be implemented via collaboration or subcontracting rather than effective recruitment of staff in this area.

The arrival of two new academic researchers, more HDRs and consequently, more PhD students will require additional space, an issue that has been raised by most personnel categories. The evaluation committee understood that a new research building will be opened in the faculty of Medicine (hosting the GRED), which may free some space in the building currently occupied by the unit.

Recommendations

The evaluation committee feels that the transition after the death of the previous director has been successfully achieved. The new director is a very competent scientist with strong track record in publication and funding (including an ANR JC/JC). The committee was pleased to observe that the new director received support from all the personnel within the unit. Obviously this is an ideal situation which should not be considered as definitely granted, and the director is encouraged to maintain such cohesion through the managerial style he has demonstrated up to now. The new director and all members should also be encouraged to maintain a high level of participation to international conferences and, whenever possible, be involved in major editorial or advisory boards.

In light of this observation, the committee cannot really recommend what the best organisational option is for the unit. The mono-team strategy seems to work and the implementation of several teams might affect the synergy and cohesion between the team members. It will be at the appreciation of the director to decide on the evolution of the unit in the future, decision that might be considered for the next evaluation.

The team is not that small since it involves about 40 members although only one is a full time researcher. Nevertheless the committee feels that the new project is extremely ambitious and has branched on several research lines. The committee will recommend that clear priorities be identified to unambiguously establish the short and mid term objectives versus the longer terms goals. The diversification of the projects should also be clearly accompanied by the identification of the personnel involved in or leading each individual topic, so that the feasibility could be documented and the internal organisation of the unit identified.

Some of the new topics are highly competitive such as microbiota (microbiota/cancer, microbiota/IBD) and a number of teams with state of the art bioinformatic facilities are specialized in microbiota studies. The committee feels that there is a risk here and encourages the director to define the niche of the unit more precisely. It is likely that if it remains *E. coli* centred, with studies on the molecular mechanisms, it will still be original and fully reliying on the expertise of the team. It is also important that the project on the role of the *clb+ E. coli* in tumours progression be clearly coordinated with other groups in France working on this very same topic.

In conclusion the committee feels that all the risks have been well mitigated, that the unit has a strong potential and the ability to train young generation of academics and clinicians at the interface of microbiology and gastroenterology.