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

Section des Unités de recherche

AERES report on the research unit

Epithelial Functions and Dysfunctions

From the

Université de Franche-Comté

March 2011



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et de l'enseignement supérieur

Section des Unités de recherche

AERES report on the research unit
Epithelial Functions and Dysfunctions
From the
Université de Franche-Comté

Le Président de l'AERES

Didier Houssin

Section des unités
de recherche

Le Directeur

Pierre Glorieux

March 2011



Research Unit

Name of the research unit: Epithelial Functions and Dysfunctions

Requested label: EA

N° in the case of renewal: 4267

Name of the director: M. AIF LAMPRECHT

Members of the review committee

Committee chairman:

M. Juergen SIEPMANN, Université de Lille 2, Lille, France

Other committee members:

M. Thomas BRUNNER, Universität Konstanz, Konstanz, Germany

M. Laurent DUBUQUOY, Université de Lille 2, Lille

M. Michael OTT, Medizinische Hochschule Hannover, Hannover, Germany

M. Michel PLOTKINE, Université de Paris Descartes, Paris

M. Stéphane ROCCHI, Université de Nice Sophia Antipolis, Nice

M. Pierre LEHN, Université de Bretagne Occidentale, Brest, CNU representative

Observers

AERES scientific advisor:

M. David DOMBROWICZ

University, School and Research Organization representatives:

M. Jacques BAHY, Université de Franche-Comté, Besancon



Report

1 • Introduction

- **Date and execution of the visit:**

The visit took place on 3rd March 2011 and included presentations of the director of the research unit as well as of some of his collaborators. The presentations were followed by discussions with the review committee. In addition, separate discussions were held with the review committee members and the following three groups of personal: (i) PhD students and postdoctoral fellows, (ii) engineers, technicians and administrative assistants, and (iii) researchers with permanent position, all in the absence of the director of the research group. Furthermore, posters were presented and allowed for an exchange between the review committee members and team members. The review committee also met the vice-president for research of the University of Franche-Comté as well as other representatives of the Faculty of Medicine and Pharmacy, University and University hospital (on 2nd March 2011).

- **History and geographical localization of the research unit, and brief presentation of its field and scientific activities**

The EA 4267 "Pharmaceutical, Biological and Analytical Sciences" was created in 2008 by the fusion of the following two teams: (1) the EA 3924 "Pharmaceutical and Analytical Sciences" and the EA 3921 "Cellular and Metabolic Optimization". The present application seeks renewal of the EA 4267, with a new title: "Epithelial Functions and Dysfunctions" and a new director. The research group has been restructured. Some of the former EA 4267 members decided to leave the group and to work in a separate team. New team members intend to join the group. The research unit is located in Besancon, at the Faculty of Medicine and Pharmacy, University of Franche-Comté. In 2012 they are expected to move from their current building into a newly constructed building. The majority of the new team members is located in Dijon, at the University of Dijon. The research project particularly focuses on the following three epithelia (1) the digestive epithelium, (2) the hepatic epithelium and (3) the vascular epithelium. The major objective is to develop new therapeutic strategies aiming at the optimization of the respective epithelial functions and the transport of xenobiotics through these barriers.

- **Management team**

The management team is limited to the director of the group.



- **Staff members**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	27	19
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	8	6
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2	
N6: Number of Ph.D. students (Form 2.8 of the application file)	16	
N7: Number of staff members with a HDR or a similar grade	19	16

2 • Overall appreciation on the research unit

- **Summary**

The research unit has been created in 2008, as the result of the fusion of two former “EA” teams. Since then major efforts have successfully been undertaken to unify the group and a common focus has been found. The group is actively publishing in peer-reviewed international journals, including the leading journals in their field. They successfully attract competitive funding and intensively collaborate with industrial partners. Also interactions with academic laboratories on the local, national and international level are very fruitful. The envisaged project is partially highly original and is risk-driven. It offers major potential to advance science in the area of innovative drug delivery systems. The research on liver aspects is more fundamental and should be rendered more innovative in the future. The director of the research unit is a member of the highly prestigious “Institut Universitaire de France” (IUF) and recognized as an opinion leader in his field. The group provides a very broad spectrum of methods and know-how in a highly interdisciplinary field. This is a major strength of the group, increasing the chances for a successful conduction of the envisaged research project.

- **Strengths and opportunities**

- Following the fusion of the two research units EA 3924 and EA 3921 in 2008, the team was able to identify and concentrate on a new focus. Thus, the group managed very well the challenging situation resulting from its history: from different fragmented groups with highly diverse research topics a new team was formed around a unified topic and a well defined focus. The new synergy was particularly clearly pointed out during the oral presentations and subsequent discussion.

- Important parts of the research conducted by the group are at the cutting edge of science. This includes the work on nanoparticulate drug delivery systems and arginase inhibitors. The proposed project is in this respect well thought of and highly original. It definitely intends to go beyond the current state of the art and is partially risk-driven. It addresses a hot topic in nowadays’ research and offers significant potential for important findings.

- The group is highly active in publishing: with only 13.5 “Full time researcher equivalents” they published 161 peer-reviewed articles in international journals since 2006 (until proposal submission in 2010). Many of these articles were published in the leading journals of the team’s research field.



- The group offers a great spectrum of methods, which are highly complementary and appropriate for the envisaged research project. This includes for example various techniques for the preparation and characterization of innovative drug delivery systems in vitro and in vivo, such as the extraction of new drug candidates from plants, emulsion methods for nanoparticle manufacturing, in vitro drug release measurements, cell culture tests, and animal models. To be able to achieve the ambitious goals, this broad spectrum is indeed needed, being located at the interface of pharmaceuticals, medicine, toxicology, biology and pharmacognosy.

- The team provides the required long term experience and know-how in the key technologies they will use to achieve their research goals.

- The group intensively collaborates with industrial partners, allowing for the transfer of new findings in more fundamental sciences into practical applications. One team member created a start-up a few years ago, which actively collaborates with the research unit.

- o The team intensively collaborates on a local, national and international level. This allows for fruitful exchange with other research groups and for the acquirement of new techniques and know-how.
- o The director of the research group is an opinion leader in his field and is member of the highly prestigious "Institut Universitaire de France" (IUF).

- In the next few years, three permanent teaching researchers will be newly appointed. This was confirmed by the Vice-president of the University of Franche-Comté and offers important opportunities to strengthen existing competences of the research unit and/or to acquire new ones.

- The team is expected to move into a newly constructed building this year, which will offer significantly improved technical standards and much more modern facilities than the building currently occupied by the group.

• Weaknesses and threats

- The scientific animation of the research team is not yet clearly defined and structured.

- The moving into the new building might take significant time and needs significant effort.

- The group must pay attention to stay focused. Otherwise, the team will not provide the required critical mass to achieve their goals. The limited size does not allow covering a broader range of research topics.

• Recommendations

- To establish an efficient scientific animation. Meetings of all team members should be regularly scheduled and well attended, allowing for intensive and coordinated exchange. PhD students and post-doctoral fellows should be given the opportunity to present and discuss their work at such meetings.

- To render the research on liver toxicology more innovative. For instance, new techniques to study nanoparticle toxicity might be developed.

- To be efficient when moving into the new building, e.g. minimizing waiting times and identifying critical risks well in advance.

- To stay focused on the identified research topic.

- To be cautious when recruiting the three permanent teaching researchers (promised by the university).

- To install an external advisory board, which could for instance once a year evaluate the progress of the team and give recommendations for the future.

- To increase the level (rather than the number) of publications by publishing in high impact factor, general journals.



- **Production results**

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	19
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	0
A3: Ratio of members who are active in research among staff members $[(A1 + A2)/(N1 + N2)]$	1
A4: Number of HDR granted during the past 4 years	2
A5: Number of PhD granted during the past 4 years	8

3 • Specific comments

- **Appreciation on the results**

The research on novel drug delivery systems is highly original and partially risk-driven. If successful, it can have a major impact in the field. This is particularly true for the investigated innovative nanoparticles for the treatment of inflammatory bowel diseases. New and promising preparation techniques are under development for this type of advanced drug delivery systems, which are loaded with different biologically active agents. Importantly, the crucial bottlenecks encountered are appropriately identified and addressed. This includes for example the avoidance of toxic organic solvents during nanoparticle manufacturing.

The research on liver aspects is more solid and comparatively less original. It is currently more used as a valuable testing platform for the toxicity of the novel types of drug delivery systems and natural compounds. It would be good to change this and to be more innovative and risk-driven in the future. For instance, the development of novel toxicological tests for nanoparticles might be envisaged. The results published so far in this area are solid, but they are not at the cutting edge with respect to the novelty of the applied techniques at the international level.

The group is actively publishing in peer-reviewed international journals. Importantly, this includes the leading journal in their field, e.g. the Journal of Controlled Release and Biomaterials. Since 2006, 161 full articles have been published (including 1 first author Nature Reviews Gastroenterology): 2 with an impact factor (IF) > 10, 14 with $5 < IF < 10$, 100 with $2 < IF < 5$, and 45 with an impact factor < 2. It has to be pointed out that the impact factors of the top journals in the group's research field are in the range of "3 to 7" only. Thus, the large majority of the articles has been published in the top journals of the group's research field. Furthermore, 1 patent application has been filed.

- The team members are also actively presenting their results at national and international scientific meetings in the form of posters and oral communications. For example, since 2006 they provided 18 invited lectures (e.g. at the 6th International Conference on Biomedical Applications of Nanotechnology), 41 presentations at international scientific meetings (with proceedings, e.g. 34th International Conference on Micro and Nano Engineering) and 45 presentations at national scientific meetings (with proceedings, e.g. Hopipharm).

- **Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners**

The director of the research unit has been appointed a member of the "Institut Universitaire de France" (IUF). This is a highly prestigious recognition in France, attributed as the result of a highly competitive selection confounding all scientific disciplines. He is considered as an opinion leader in his field, also on an international level. The other team members are less visible.



A considerable number of young scientists (master/PhD students/post-doctoral fellows) is trained in the group. For instance, 8 PhD degrees and 2 “Habilitation” degrees (“HDR”) were obtained by team members since 2006 until the proposal submission in 2010. Several young scientists come from abroad, however, the majority is recruited locally.

The team successfully applies for external, competitive funding. Two ANR projects and a BioAsia project (funded by the French ministry of Foreign Affairs) are ongoing. Furthermore, the Institut Universitaire de France supports the research work of its member (the director of the group).

The group successfully collaborates with other research teams on a local, national and international level. This includes academic collaborations, for instance with the University of Madrid (Spain), the Swiss Federal Institute of Technology (Suisse), the University of Ottawa (Canada), the University of Montreal (Canada), the Hacettepe University (Turkey), the Southern Cross University (Australia), and the Freie Universität Berlin (Germany) In addition, several industrial collaborations are ongoing, involving small and medium sized enterprises, but also big pharmaceutical companies. These collaborations are either “real” collaborations, or “research services”, which help funding the group’s general research activities and allow for the transfer of new knowledge obtained in more fundamental sciences into practical applications.

- **Appreciation on the management and life of the research unit**

The management of the research unit is not yet clearly defined. It will be important to establish an efficient scientific animation, including regular meetings of all team members. The fact that many team members were absent during the visit of the review committee, without any explanation, is an example, which indicates the need for an improved organization of the team. The willingness of the team members (which were present during the visit) to form a common and active team was clearly visible. The young scientists are well supervised by the permanent researchers. The emergence of cutting edge research projects is well supported in the team.

All permanent team members have considerable teaching duties; some of them also provide services in the University hospital. Several team members are actively involved in the local “Federative Research Structure”, e.g. via technical platforms, and significantly contribute to the interactions of the local research players, in particular the University hospital.

- **Appreciation on the scientific strategy and the project**

The envisaged project is sound, partially highly original and feasible in the context of the unit. The planned work on nanoparticulate drug delivery systems and arginase inhibitors is highly original and partially risk-driven. It has major potential to advance science beyond the current state of the art. In contrast, the envisaged work on liver aspects is more solid and less original, thus, continuing the same level of the group’s past research work in this domaine. The provided skills and equipment are essentially to be used as a valuable testing tool for the toxicity of the novel types of drug delivery systems and of natural compounds. It is not really envisaged to address the methods themselves and to render them more innovative.

Most of the allocated resources are bound to specific projects. The recurrent, basic funding is relatively limited and appropriately distributed within the group, including the support of novel, risk-driven initiatives.

Highly original, cutting edge projects are ongoing, new ones are envisaged in the future and they are - according to the available funding - appropriately supported. More risk-born projects could be developed in the field of liver toxicology (e.g. using stem cells) and in the area of reduction, refinement and replacement of animal testing (3R).

The discussions with the review committee members clearly demonstrated the ability of the team members to adequately build their research strategy and to question it, considering the up-to-date literature.



Intitulé UR / équipe	C1	C2	C3	C4	Note globale
FONCTIONS ET DYSFONCTIONS ÉPITHÉLIALES (FDE)	A	A	A	A	A

- C1 Qualité scientifique et production
- C2 Rayonnement et attractivité, intégration dans l'environnement
- C3 Gouvernance et vie du laboratoire
- C4 Stratégie et projet scientifique



Statistiques de notes globales par domaines scientifiques
(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2_LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	42	5	20	26	36	59	5	17	29	239
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

* les résultats SVE2 ne sont pas définitifs au 06/05/2011.

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

- **SVE1 Biologie, santé**
 - SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie
 - SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes
 - SVE1_LS3 Biologie cellulaire, Biologie du développement animal
 - SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie
 - SVE1_LS5 Neurosciences
 - SVE1_LS6 Immunologie, Infectiologie
 - SVE1_LS7 Recherche clinique, Santé publique
- **SVE2 Ecologie, environnement**
 - SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement
 - SVE2_LS9 Sciences et technologies du vivant, Biotechnologie
 - SVE2_LS3 Biologie cellulaire, Biologie du développement végétal

UNIVERSITE DE FRANCHE-COMTE

PRESIDENCE

UNIVERSITÉ DE FRANCHE-COMTÉ



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S2UR120001789 fonctions et
dysfonctions épithéliales 0251215K

Personne chargée du dossier :

Christiane GRILLIER

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BORDEREAU DES PIECES ADRESSEES A :

AERES

Comité d'évaluation de l'EA 4267
Fonctions et dysfonctions épithéliales

DESIGNATION	OBSERVATIONS
- volet général : observations générales sur le rapport d'évaluation de l'EA 4267	Pour attribution

Besançon, le 20 avril 2011

Le Président de l'Université,



S2UR120001789 FDE 0251215K

**Volet général : observations générales sur le rapport d'évaluation du laboratoire
Fonctions et dysfonctions épithéliales (FDE).**

Dear Ladies and Gentlemen,

We have been carefully reading the evaluation report on our research group FDE and are thankful to the jury members for their remarks and recommendations which we take into account for our future research project.

We have been particularly sensible concerning the comment on the scientific animation of our future research group, especially in the training our young researchers.

The assessment of the strategic setup of the research proposal revealed that the jury considered the axis 'hepatic epithelium' as lacking of originality for future advancements. We believe that our presentations did not sufficiently underline the innovative character of the project 'hepatic stem cells' within this axis. The acquired funding within the excellence cluster 'therapeutic innovation' (Strasbourg) and the support by "Oséo" should build a reliable basis for this project. Besides, a postdoctoral fellowship on nanoparticle interaction with hepatocytes that has been obtained in the 2011 will enhance the innovative research in the axis 'hepatic epithelium' in the context of the transdisciplinary research focus of our group for the next five years.

Sincerely yours,

Alf Lamprecht
Director