Fonction structure et inactivation d'ARN bacteriens

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Fonction structure et inactivation d'ARN bactériens

From the

University Rennes 1

INSERM

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

December 2010

Research Unit

Name of the research unit: Fonction structure et inactivation d'ARN bactériens

Requested label: UMR_S INSERM

N° in the case of renewal: U835

Name of the director: M. Brice FELDEN

Members of the review committee

Committee chairman

M. Knud H. NIERHAUS, Max Planck Institute, Berlin, Germany

Other committee members

M. André GERBER, ETH, Zurich, Switzerland

M. Philippe CHAVRIER, Institut Curie, Paris, France

Committee members suggested by CNU, CoNRS, CSS INSERM, CSS INRA, INRIA, IRD

Ms. Marié-José BUTEL, University Paris 5, Paris (CNU)

M. Thierry NAAS, University Paris 11, Paris, France (CSS5 INSERM)

Observers

AERES scientific advisor

Ms. Catherine DARGEMONT

University, School and Research Organization representatives

Ms. Christine TUFFEREAU (INSERM)

Report

1 • Introduction

- Date and execution of the visit

The visit occured at the 8th December 2010 from 14:00 to 16:30. The director gave a short overlook about the history and organization of the group and afterwards described the scientific activities in the past and the already achieved results concerning their current and future main topic, namely non-coding RNAs and their relationship to the virulence of S. aureus. After a 30 min scientific discussion we met PhD students and postdocs, engineers technicians, administrative assistants, and permanent researchers, and we discussed issues of group management. The visit finished with a 30 min discussion with the director alone. Then some aspects of the managemnt of the group were discussed with representatives of the university and INSERM.

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

The research unit is located at the faculty of pharmacy, Rennes. This research unit studied the function and structure of the bacterial transfer-messenger RNA (tmRNA). This RNA, only present in prokaryotic cells, is responsible for unblocking ribosomes stalled on problematic messenger RNAs. Two additional projects dealt with (i) development of conjugates working against hepatitis C virus (HCV) and (ii) the detection and analysis of non-coding RNAs in the human pathogen Staphylococcus aureus that play probably a role in virulence.

- Management team

Due to the small size of the research-unit the management team consists only of the director and the secretary.

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4	5
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)	4	5
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	3
N7: Number of staff members with a HDR or a similar grade	2	3

2 • Overall appreciation on the research unit

- Summary

In all three fields (tmRNA, compounds against HCV and non-coding RNAs in Staphylococcus aureus) the group has developed ingenious ideas and originality in the design and performance of the experiments. A main feature of the group is their strict focus on relevant research goals. They identify problems to be solved and do not hesitate to collaborate with leading groups in order to increase their research impact. Another point pertinent to this aspect is that they do not hesitate to stop a research track, if they recognize a scientific dead end. All these points result in a high scientific impact of the group well recognized by corresponding scientific communities. In topics "trans-translation" and non-coding RNAs in S. aureus they belong to forefront players internationally. It is noteworthy that the achieved results and the future plans are well presented.

- Strengths and opportunities

The work of the unit greatly improved the knowledge on the trans-translation and described new RNAs in S. aureus. The latter research is of great interest in both basic knowledge and translational regulation. These RNAs could lead to interesting novel targets for diagnostic purpose and anti-staphyloccocal drugs. This unit has already a recognized expertise concerning this theme. The current strength of this unit is the future focus on non-coding RNAs of the human pathogen S. aureus. Another positive feature is seen in establishing various collaborations, allowing them to accelerate and deepen the investigations.

- Weaknesses and threats

The group would certainly benefit, if a full-time scientist could join. We also consider the absence of PhD students and postdocs from abroad as a disadvantage.

- Recommendations to the head of the research unit

In the context of the already obtained impressive results we recommend to consider an implementation of a study on the epidemic appearance of new S. aureus strains and to check them for specific expression of non-coding RNAs. These RNAs could play a prominent role in the virulence of these subspecies and thus could be an important contribution to the already selected RNAs. Overall we consider the experimental strategy as highly attractive. Recruitment of people from abroad would have the important consequence that lab-meetings should be held in English. In general, people of the lab seem to be isolated from international science, e.g. obligatory Journal Club meetings could help. Group leader could apply to Institute Universitaire de France to dedicate more time for research.

- Production results

The scientific production of this small unit is at a very high level, with 24 publications between 2005 and 2010, 18 of which with the director as last author. Most of the pubications appeared in journals with a good or high impact factor (Nucleic Acid Research, PNAS, EMBO Report, PLoS Pathogens…). Moreover, two patents have been obtained.

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	4
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	1
A5: Number of PhD granted during the past 4 years	4
A6: Other relevant item in the field *(i.e. number of first and/or last authors original publications in peer review journals)*	16

3 • Specific comments

- Appreciation on the results

The research unit pursued three objectives:

1: Principles and mechanisms of trans-translation.

In the center of this bacterial emergency system stands tmRNA, a monster of about 350 nucleotides with an mRNA and a tRNA module, the latter can be charged with Ala. This system rescues ribosomes stuck at the end of a fragmented mRNA lacking a stop codon. Binding of tmRNA to the decoding center in the absence of a codon requires a special factor SmpB, the binding is supported by EF-Tu and the ribosomal protein S1. During the last research period the research group has made important contribution, examples are: (i) SmpB mimics the lacking codon-anticodon interaction, usually codon-anticodon interaction is an absolute requirement for a tRNA binding to the ribosomal A site; (ii) SmpB co-migrates with the tRNA module through the ribosome (together with colleagues from Moscow); (iii) S1 supports tmRNA binding; (iv) single particle reconstructions of 70S•tmRNA complexes via cryo-electron microscopic, first with a group in New York, later with local colleagues. These achievements demonstrated how SmpB is mimicking codon-anticodon interaction and showed how this monster occupies the A site and is translocated to the ribosomal P site. In summary, the results have significantly broadened our knowledge about this important bacterial emergency system. This topic has been now forwarded to the group of a former colleague, who is also an expert of trans-translation.

2: Constructing and testing some compounds fighting HCV (hepatitis C virus).

The group pursued the promising concept of developing an oligo-DNA complementary to an initiation site of HCV and carrying at one side an imidazole residue capable of cleaving the virus RNA. One of the compounds showed hydrolysis activity at low concentrations in vitro and antiviral activity in vivo. However, a dose-dependent effect observed in vitro could not be reproduced in vivo. For this reason the experimental line was abandoned.

3: Small RNAs (sRNAs) in Staphylococcus aureus.

Staphylococcus aureus is an important pathogenic bacterium in man. Small regulatory RNAs (sRNAs) seem to play important roles for the pathogenicity and virulence of this bacterium. In a pioneering paper (PNAS, 2005) the group has identified 13 sRNAs mainly expressed from so-called pathogenicity islands of the genome, loci that are known to code for many virulence factors. For this reason the group concentrated their research on the possible roles of sRNAs in causing diseases. Therefore, they have established a whole arsenal of techniques for disruption of sRNA genes, complementing this KO strains via expressing the corresponding sRNA from plasmids, and eventually overexpressing sRNAs. They further master methods to judge the phenotype of the mutated/altered strains including

an animal model (mice). As published 2009 the activity of certain sRNAs in S. aureus does not seem to involve the Hfq RNA-binding protein. Although a negative result, it is interesting that at least some sRNAs appear not to depend on Hfq in S. aureus, since a myriad of RNA effects in E. coli and other bacterial strains are known to involve Hfq. Recently they published another set of 14 sRNAs and could show, that one sRNA was involved/responsible for disease in a mouse model of infection. This topic has now become the main interest of the research group. The group therefore has an excellent position to analyze the selected non-coding RNA with respect their molecular functions and role in virulence.

The scientific production of this small unit is at a very high level, with 24 publications between 2005 and 2010, 18 of which with the director as last author. Most of the publications appeared in journals with a good or high impact factor (Nucleic Acid Research, PNAS, EMBO Report, PLoS Pathogens,…). Moreover, two patents have been obtained.

The group has a number of stable collaborations: three local, three national and one international.

- 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 obtained several awards during the last years (e.g. First prize of the "National Academy of Medicine" in 2008, and Medals of the city of Rennes in 2005 and 2006). He is also regularly invited to international conferences. In 2007, the group has been elected to be an monothematic INSERM research unit.

Two of the former colleagues obtained professor positions, one of them is at the Rennes University.

The group was successful with three recruitments (two in 2009, one in 2010). In particular, the recruitment of a PU-PH should be mentioned, who has an impressive list of publications and has a position in a hospital, which is interesting regarding the project of the team. Most of the researchers appear to be of French nationality – possibly a bit more international mixture may be an advantage.

The research unit is able to raise substantial funding.

- Appreciation on the strategy, management and life of the research unit

We suggest a future recruitement of foreign coworkers with the consequence of having a regular literature seminar in the group in English, which might have an important impact concerning scientific animation. We also suggest (if applicable) to keep regular scientific group meetings in English to train presentation skills for an international audience. Sending PhD students at the end of the thesis period and postdocs oaccasionally to international conference will further improve the scientific training of the group members. The same is true for sending the students abroad in the frame of international exchange programs.

Many staff members participate in the heavy teaching load of the group.

- Appreciation on the project

As mentioned above already the study of sRNAs from S. aureus will be at the center of the scientific activity of the group. Now we know that about 92 RNAs are expressed in this pathogenic bacteria. The group, however, will concentrate their human resources on less then 10 RNAs most of them are expressed from pathogenicity islands. Each member of the group will study one RNA, so that progress can be expected on a broad front, a point that appears to be necessary facing the strong international competition. Strategically they will proceed on four levels: at the atomic level trying to solve the structure of RNAs and their complexes via NMR, X-ray and cryoEM; at the molecular level trying to identify RNA ligands; at the cellular level working with fluorescence labeling in situ; and at the animal level studying infections in their mouse model. Due to the high genomic plasticity of S. aureus they will analyze for each RNA more than one strain of S. aureus to avoid strain-specific effects. They plan to start the experiments by studying expression profiles of the selected RNAs under various growth conditions in order to obtain first hints about the "physiological value" of the RNAs. Then the importance of the individual sRNAs should be unraveled according to the four levels mentioned above, and for each level sound procedures are suggested with techniques, which are either mastered by the group or where "proof-of-principle" experiments have been performed already. All the expected results have the potential to merge towards a development of both diagnostic tools for S. aureus infections and novel drugs against infections.

This is a sound and straightforward project of excellence, logically designed and well presented. The experimental basis is very broad and at the same time definitions of scientific goals are focused. The project could become of great medical relevance as the development of drugs that specifically interfere with selected sRNAs could be used as « novel » antibiotics. In this regard, the unit already holds two patents and more may come along with further research on sRNAs.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
FONCTION STRUCTURE ET INACTIVATION D'ARN BACTERIENS	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**

PRÉSIDENCE

Guy Cathelineau
Président

UNIVERSITÉ DE RENNES 1

Rennes, le 24 février 2011

Monsieur Pierre GLORIEUX
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Fonction Structure et Inactivation d'ARN bactériens –
0350936C

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 mixte de recherche « **Fonction Structure et Inactivation d'ARN bactériens** ».

L'université de Rennes 1 sera particulièrement attentive à ce que les recommandations formulées par le comité de visite soient prises en compte.

A la lecture de ce rapport, qui atteste de l'excellence de l'activité scientifique conduite au sein de cette unité de recherche, le Professeur Brice Felden, directeur de cette unité, nous a indiqué qu'il n'avait pas de remarques particulières à formuler sur ce rapport très positif.

L'Université de Rennes 1 souscrit en totalité à cet avis et promeut également l'idée que cette unité de recherche de petite taille s'insère plus globalement dans la dynamique de structuration renforcée du secteur de recherche Bio-Santé menée en partenariat avec le CHU et l'INSERM par l'Université sur le campus Villejean.

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

Le Président de l'Université de Rennes 1

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