Virulence bactérienne et maladies infectieuses

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Virulence bactérienne et maladies infectieuses

Under the supervision of the following institutions:

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

Nouvelle Université de Montpellier

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 Eric CASCALES, 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

Unit name:	Virulence Bactérienne et Maladies Infectieuses
Unit acronym:	
Label requested:	INSERM
Present no.:	U 1047
Name of Director (2013-2014):	Mr David O'CALLAGHAN
Name of Project Leader (2015-2019):	Mr David O'CALLAGHAN

Expert committee members

Chair:	Mr Eric CASCALES, Université Aix-Marseille, Marseille
Experts:	Mr Tom COENYE, Université de Gand, Belgique
	Mr Jean-Jacques LETESSON, Université de Namur, Belgique
	Mr Philippe MOREILLON, Université de Lausanne, Suisse
	Ms Marie-Cécile PLOY, Université de Limoges (representative of the INSERM CSS)
	Ms Astrid VAN DER SAR, Université d'Amsterdam, Pays Bas

Scientific delegate representing the AERES:

Ms Sophie DE BENTZMANN

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

Ms Stéphanie POMMIER, INSERM

Mr Michel DESARMENIEN (Representative of Doctoral School N°168)

Mr Jacques MERCIER, Université de Montpellier 1

1 • Introduction

The "Virulence Bactérienne et maladies Infectieuses" (Bacterial virulence and infectious diseases) unit is an INSERM unit (U 1047) affiliated to the University of Montpellier 1. This unit reunifies three entities with distinct research topics or themes, two of which being interested in fundamental microbiology (*Brucella* and *Burkholderia*), and one related to clinically-oriented research (diabetic foot ulcers). The AERES visit on site has been organized on January 30th, 2014. The scientific program included an overall presentation of the unit by the unit director, describing its history and achievements as well as the past and future organization. This presentation was followed by 3 scientific presentations of the past activity and projects of the three main topics developed in the unit. The director of the unit presented the work of the *Brucella* group and the work on diabetic foot ulcers, while the work on the *Burkholderia* group was presented by the principal investigator in charge of this thematic. Additional meetings with (i) researchers with permanent positions (ii) PhD students and post-doctoral fellows, (iii) engineers, technicians and administrative staff and (iv) representatives of the Montpellier University and INSERM administrations were also organized.

History and geographical location of the unit

The U 1047 was created in its current form in 2011. The unit is attached to the Université Montpellier 1, and is located in the Nimes campus of the Faculté de Médecine and Nimes University Hospital.

Management team

The U 1047 unit is headed by Mr David O'CALLAGHAN, each research theme (or subgroup) being directed by a permanent researcher. The unit has no laboratory council *per se* but all the members of the unit participate to a weekly laboratory meeting in which information on the life of the unit are shared and discussed.

AERES nomenclature

SVE1_LS6 Immunologie, microbiologie, virologie, parasitologie

SVE1_LS7 Epidémiologie, santé publique, recherche clinique, technologies biomédicales

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	3	3
N2: Permanent researchers from Institutions and similar positions	3	3
N3: Other permanent staff (without research duties)	3	2
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	2	1
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)	3	3
TOTAL N1 to N6	**14**	**12**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	5	
Theses defended	3	
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	5	5

2 • Assessment of the unit

Global assessment of the unit

The U 1047 unit is a small-size INSERM unit, associated with the Montpellier University and closely associated with the Nîmes hospital, a number of permanent researchers of the unit being PH (Practicien Hospitalier, Medical Doctor). The research is divided in three distinct themes: two fundamental research themes closely related (mechanisms involved in the virulence of *Brucella* and *Burkholderia*) combined with a clinically-oriented theme dedicated to Diabetic Foot Ulcers and *Staphylococcus*. There are a number of connections between the fundamental and clinical research but these connections might be strengthened by additional collaborative projects.

Although the general output of the unit in terms of publication and presentations at international meetings is good, there is clear imbalance between the three research themes. The fundamental research groups are well represented at international meetings and are well-known but the level of publication (both in terms of number of published articles and of impact) is low. By contrast, the clinical research group is publishing at a higher level but is less present at international meetings (apparently there is a focus on national meetings). In general, the atmosphere in the unit appears to be excellent. The unit has access to specialized equipment for developing their studies (biosafety L3 for work with the bacterial pathogens, fish tanks for the zebrafish model, access to clinical samples through the strong involvement of the clinicians at the hospital).

Strengths and Opportunities

The unit gathers a number of renowned scientists and medical doctors. Within the three themes, the research focusses on both the bacterial and the host side, which is a strength and helps to better understand the relationships and cross-talks during infection. Clinicians have direct access to samples from the hospital and the unit is well equipped with BS3 facility and fish tanks. A number of internal and external collaborations are already in place. Although the clinical theme seems a bit disconnected from the two other groups (which might be a weakness, see below), it is also a strength to have such a strong connection with the hospital (which may support the wish to keep the research on site rather than joining existing units in Montpellier) and to have complementary expertise.

The unit director has an excellent scientific network and is internationally well-known. One example of this is the fact that several members of the unit have been recently asked to write review papers and book chapters, which clearly indicates the acknowledged expertise by the scientific community. The expertise of the Director on *Brucella* has promoted the unit to host the reference center for *Brucella* and brucellosis (Centre National de Reference).

Weaknesses and Threats

The link between fundamental and clinical researches is not clear or insufficient. Although there is "Zebraclub" meeting, the relationships with other units in the Montpellier/Nîmes area are limited.

One threat is the lack of funding for the next couple of years as most public financing and industrial contracts have already come to an end. Although there is substantial funding from the INSERM and the University of Montpellier, external funding is unsecure.

The restriction from the French system (ANR, HDR, limited number of PhD students) is also an external threat and therefore the members should recruit abroad. As a consequence, only 3 PhD theses have been defended during the previous period and 4 are ongoing – which is not overwhelming. It is worthy to note that none of the unit members are part of the doctoral school council or participate in the selection committee for PhD fellowships. There is a clear need to be better connected with the University of Montpellier.

The number and impact of the publication is limited, especially for the two fundamental groups. For example, two of the PhD students who defended during the previous period published a single article (1 FEBS Open Bio as 1st author in 2012 for the first, 1 publication in J Infect Dis in 2012 as 3rd author for the second), while the third one did not get yet publication. A similar situation is found for the INSERM researcher in the *Brucella* group, who published one article since her arrival in the unit (last author in Microbes infect). Regarding visibility and attractivity, the clinical group (and to a lesser extent the *Burkholderia* group) should increase their international visibility.

Regarding the project proposed, there is clearly a lot of ideas but the focus is missing. This is particularly obvious for the *Brucella* group for which the future developments are simply unrealistic compared to the available manpower.

Recommendations

The committee recommends that a global and more integrated strategy is defined for the evolution of the unit in the coming years. This is particularly important to strengthen the links between the fundamental and clinical researchers, not only by increasing the discussions between members (it is clear that this already happens) but by developing collaborative projects.

The younger theme leaders should improve their visibility by participating to international conferences. Notably, the members of the *Burkholderia* theme should participate to more general meetings on cell biology to acquire expertise in this field and to improve their visibility and attractivity. Members of the clinical group are recommended to participate more actively to international meetings rather than being limited in the French or French-speaking area.

The productivity of the unit should be also improved by dedicating the available manpower to focussed lines of research. Raising funds to develop the team is also an important goal to achieve. The theme leaders are however aware of this and already postulated to financing agencies, but there is a critical need to be more aggressive on this, not only at the national level but also at European agencies..

The committee also encourages the unit to host more PhD students. This can be achieved by developing more connection with the University of Montpellier (higher involvement in the teaching activities, access to the Doctoral School council).

The projects are dedicated to understand the molecular basis underlying microbial infections, and therefore deal with both the bacterial and eukaryotic host sides. The unit should consider reinforcing the expertise on cell biology/immunology by attracting or recruiting talented young scientists. If this has already been done with the arrival of a PI, the committee encourages the unit to pursue this path to have equilibrated microbiology/cell microbiology/clinical experts.

3 • Detailed assessments

Assessment of scientific quality and outputs

During the period under review the scientific output has been of good standard but no real breakthrough has been made (such as that deserving publication in high ranked general journals). This could be expected based on the relevance of the studied models and on the quality of the researchers gathered in this unit.

Taken together, the overall publication level of the unit could be considered as satisfactory. However, the heterogeneity is rather high. Clinical research produces a prominent part of the unit's publications. The publication level is situated between 5 and 10 publications per year (which represents an average of 1 publication per permanent researcher) and with impact factors situated, in average, between 2 and 6 (J Infect Dis, PLOS Pathogens, Blood, FEBS Lett, PLOS ONE, Clin Microbiol Inf, Diabetes Care, BMC Med, Infect Immun, J Bacteriol, Antimicrob Agent Chemother,…).

During the previous period, there was a good ability to raise funds (grants from ANR, FRM and VLM and funds from private companies). The European FP7 program was not a major funding source, although the unit director should consider this possibility based on his international recognition. The clinical research is not well funded by public agencies and does not seem to be overwhelmingly funded by the industry either. Although the overall funding was good, the future funding situation is unsecure as all the grants already finished.

Assessment of the unit's academic reputation and appeal

The unit director has an excellent networking and participates to a significant number of conferences. The international recognition is also indicated by the invitation to write reviews and book chapters (including as guest editor for an issue in Curr. Opin. Microbiol.). The leader of the *Burkholderia* team is well known in the field of secretion systems and starts to be recognized in the *Burkholderia* field (*e.g.*, participation to the International *Burkholderia cepacia* Working Group) which is significant compared to the relatively limited number of years working on the topic. There is a need to participate to more general conferences related to bacterial pathogenesis to have a broader recognition. On the other hand, clinical scientists are much more often participating to national meetings and efforts should be made to increase the involvement of the members of this team at the international level.

Regarding academic attractivity, a relatively low number of theses have been defended during the past period, and a limited number of PhD students are currently working in the unit (with the exception of the *Burkholderia* team, see below). However, although this number seems limited, discussion with the representative of the doctoral school showed that the unit is doing well and that the number of PhD students is above average compared to other units belonging to the University of Montpellier. The attractivity for external PhDs or post-doctoral fellows is very low (except visitors involved in collaborative projects) and one may expect to see more foreign young researchers joining the unit with an increased participation to international meetings and with an increased publication rate.

The committee however recommends to develop more links with researchers in the Montpellier' area. It appears that a few connections already exist (such as the Zebrafish journal club) but these need to be strengthened. The unit has also connections with the Maison-Alfort veterinary institute.

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

The unit has a strong link with the hospital of Nîmes, thanks to the clinical research, and has good interactions with private companies due to the health problems engendered by the bacterial models. A number of unit's members participate as experts for funding agencies or serve in Scientific Advisory Board of biotechnology companies. The unit hosts the National Reference Center for Brucellosis since 2012.

Assesment of the unit's organisation and life

The life and organization of the unit is excellent, and seems very democratic even though there is no laboratory council. Organizational, hygiene and safety, and strategic discussions are brought during the weekly seminar. All the questioned members of the unit felt that the organization is excellent and are very enthusiastic about working in this environment. Due to the isolation of the unit on the Nîmes campus in the Montpellier area, the interactions with other research units in Montpellier are rather limited. Maybe the unit should organize more regularly

seminar series with invited speakers. A secretary position has been recently filled in by the INSERM. This was obviously an important requirement as the researchers of the unit were burden with administrative work. The unit is also supported by the Montpellier University, as shown by the recent obtainment of a permanent engineer position.

Assessment of the unit's involvement in training through research

The number of PhD students in the unit is rather limited. This is however partly due to the French system which limits the number of students (PhD per HDR, no PhD contract with ANR funding, lack of fund to pay trainees,…). As detailed above, it seems however that the number of PhD is above average compared to other units.

Although the members of the unit perform a significant level of teaching and/or are involved in several councils at the university, the unit is not strongly involved in leading licence or master degrees (with the exception of one PI). The committee recommends to the members of the unit to participate to the activities of the doctoral school (ED 168 Sciences Chimiques et Biologiques pour la Santé), such as being elected to the doctoral school council.

During the last years, the unit has been quite involved in training undergraduates (third year of Licence or ERASMUS), but this has been limited by the recent French laws regarding training periods.

Assessment of the five-year plan and strategy

The overall strategy is considered as good. Each theme will develop interesting studies but one may recommend to consolidate the links between fundamental and clinical researches. If the strategic goal of the unit is to foster translational research, one would expect more horizontal interactions between members of each team.

The projects are considered as good, although specific criticisms and recommendations will be developed below (prioritizing projects for the *Brucella* team, developing state-of-the-art techniques for the diabetic foot ulcer team).

Because of the recent developments toward the zebrafish model, there is a clear need to increase the overall cell biology expertise of the unit. The unit should therefore consider attracting or recruiting skilled young researchers with expertise in cell biology/immunology.

4 • Theme-by-theme analysis

Theme 1 : *Brucella* and brucellosis

Manager's name : Mr David O'CALLAGHAN

Workforce

Theme workforce in Full Time Equivalents	As at 30/06/2013	As at 01/01/2015
FTE for permanent professors	1	1
FTE for permanent EPST or EPIC researchers	2	2
FTE of other permanent staff without research duties (IR, IE, PRAG, etc.)	2	1
FTE for other professors (PREM, ECC, etc.)		
FTE for postdoctoral students having spent at least 12 months in the unit	1	
FTE for other EPST or EPIC researchers (DREM, etc.) excluding postdoctoral students		
FTE for other contractual staff without research duties		
FTE for doctoral students	1	
TOTAL	**7**	**4**

• Detailed assessments

This team develops projects on the *Brucella* genus. Among the current and future prospects, particular attention is paid on the Type IV secretion system (T4SS) and potential effectors delivered by this machinery, the analysis of *Brucella* genome sequences, the identification and function of small regulatory RNAs on the bacterial side, and the role of host proteins, such as CD98 or the v-ATPase, which are parasitized during *Brucella* infection, or the identification of host factors using large-scale RNA interference screens.

Conclusion

- ***Summary:***

The team, and more specifically the theme leader, is internationally recognized and highly respected in the *Brucella* field. The group has a long experience with this bacterium and the theme leader is extremely efficient in networking at both the national and international levels. The visibility of this subgroup is therefore high on the international scene, at least in the fields of *Brucella*, bacterial secretion systems and bacterial pathogenesis.

By contrast, the number of peer-reviewed publications during the previous period is rather low, considering the international visibility of the subgroup. Based on the scientific quality of the members of the subgroup, it is expected to publish more studies, and in higher impact journals.

Regarding the projects, the committee noticed that too many projects are developed. Although this reflects the fact that the leader has tons of ideas and that many areas on *Brucella* research need to be covered, the size of the team is currently not appropriate to follow all these projects efficiently. It would be probably better to focus on specific projects to ensure efficient publication rate rather than diluting the manpower and the efforts. As it stands, the feasibility of all these projects seems unrealistic and the manpower is not sufficient to be competitive on all these subjects. However, it is interesting that the second permanent scientist in the group, has the possibility to lead her own line of research.

- ***Strengths and Opportunities:***

- The subgroup has excellent networking.
- The subgroup has a strong international recognition and expertise on *Brucella*. The recruitment of two permanent scientists (INSERM researcher and Engineer) has been achieved during the previous period.
- There is a complementary expertise between the subgroup members.
- The subgroup has developed up-to-date technologies.

- ***Weaknesses and threats :***

- There is a limited number of publications.
- There are too many projects developed without sufficient manpower.
- There is a limited number of PhD students.

- ***Recommendations :***

- The excellent networking of the theme leader should be actively pursued.
- The number of projects on the theme should be restricted to a limited line of studies. This diversity of projects is unsustainable, and the subgroup needs to focus much more. They must identify a selected number of topics and focus on these topics to ensure that they gain and maintain a niche and an international identity in the field. Importantly, this subgroup must focalize its activities to ensure it does not become outcompeted by other groups in the world. May be focusing on the relationship between T4SS and outer membrane vesicles, and on the host side (host specificity determinants, CD98) will be better, without putting too much effort (right now) on the OMIC and high-throughput (small RNA screen, RNAseq/proteome screens,…) approaches or on the T4SS effectors which is clearly a competitive field in absence of additional manpower.
- Strategies to secure future funding should be developed.

Theme 2 : *Burkholderia cepacia* complex infections

Manager's name: Ms Annette VERGUNST

Workforce

Theme workforce in Full Time Equivalents	As at 30/06/2013	As at 01/01/2015
FTE for permanent professors		
FTE for permanent EPST or EPIC researchers	1	1
FTE of other permanent staff without research duties (IR, IE, PRAG, etc.)		
FTE for other professors (PREM, ECC, etc.)		
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	**3**	**1**

• Detailed assessments

This team is focused on the virulence of *Burkholderia cenocepacia*, an organism associated with diverse pathologies including cystic fibrosis. During the previous period, the activity of this group has been centered on the development of technological tools, such as the zebrafish model (transgenic reporter fishes, RNA interference and morpholinos, *in situ* and immune labeling) and the genetic engineering of *Burkholderia*.

- ***Summary :***

The focus has been on the development of new tools. These recent technological developments have been very successful and although the publication and funding outputs are limited, the team has gained international recognition in the *Burkholderia* field as shown by the participation of group members to the meetings of the International *Burkholderia cepacia* Working Group (in fact the theme leader is organising the next meeting of this Working Group in Nimes in April 2014). Although the output is not yet very high, it is clear that these developments will lead to an increased activity in the near future and that the subgroup will benefit of these technologies to ask specific questions related to *Burkholderia* pathogenesis, both on the bacterial and host sides.

The subgroup has also been very successful for the recruitment of PhD students and has already started collaboration projects with other internationally-recognized *Burkholderia* groups worldwide. The quality of research is very good and is expected to grow thanks to the tools available. The level of publication remained low during this intermediate period but the new technologies should lead to important contributions in the future. The zebrafish research needs to be valorized, for exemple by increasing the participation to zebrafish-specific meetings or to

general cell biology meetings, or by writing a review on this virulence model. These will allow to increase the visibility and the attractivity of the subgroup and of the theme leader.

It is interesting for this subgroup to develop both its own research projects and collaborative works with other laboratories interested on the zebrafish as a virulence model. However, the theme leader should be careful to restrict the number of collaborations or to maintain a balance between proper projects/collaborations to prevent becoming a technical facility.

The committee members were very enthusiastic on the technological developments and very optimistic regarding the fate of this subgroup.

- ***Strengths and Opportunities:***

- Highly valuable technological tools have been developed in the recent years.
- Important, straightforward and focused projects are currently developed.
- The effort to develop state-of-the-art methodologies is pursued (*e.g.*, flow cytometry coupled to RNA sequencing).
- The subgroup has a visibility in the *Burkholderia* field.
- Participation to the highly competitive Marie Curie ITN program has to be noticed.

- ***Weaknesses and Threats:***

- There is a low level of publication but the outcome is expected to increase.
- Funding needs to be extended to maintain the research flow and follow up on the data in preparation.
- It is not clear whether the group has all the necessary expertise to tackle questions related to host innate immunity.

- ***Recommendations:***

- Strategies to secure future funding should be developed.
- There is a need to increase the visibility and attractivity, notably on the zebrafish expertise.
- The subgroup should carefully examine future developments, and keep a good balance between independent research and facility-like technical/collaborative works.
- The subgroup should consider attracting and recruiting a young researcher (long-term post-doctoral fellow or permanent position) with expertise on cell biology/immunology to strengthen the studies on the host.

Theme 3 : Bacterial virulence and multidrug resistant bacteria

Manager's name: Mr Jean-Philippe LAVIGNE

Workforce

Theme workforce in Full Time Equivalents	As at 30/06/2013	As at 01/01/2015
FTE for permanent professors	2	2
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.)	2	2
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	3	3
FTE for doctoral students	1	
TOTAL	**8**	**7**

• Detailed assessments

This subgroup is dedicated to understand the bases of the development of diabetic foot ulcers by identifying pathogens that play a role during the infection process, the role of phages/prophages in the attenuation of *Staphylococcus aureus* and the host responses triggered by the pathogens. The subgroup is mainly composed of medical personnel.

Conclusion

- ***Summary:***

The questions and the three main lines of research are relevant to better understand the infection processes complicating diabetic foot ulcers. The subgroup has performed very well during the previous period, including numerous publications, participation in several meetings and in cooperation networks. Although the local and national visibility is excellent, the team members deserve to be internationally recognized and this could be improved by increasing the participation to international, english-speaking, meetings.

- ***Strengths and Opportunities :***

- There is a good local and national visibility on diabetic foot ulcer.
- Very good level of publication has been reached.

- The subgroup proposes straightforward and feasible clinical research projects (metagenomic approaches, rosa-like phages, host responses) that might turn to be useful for diagnosis and therapy.
- There is a pending patent.
- The subgroup has strong connections with the hospital of Nîmes.

▪ ***Weaknesses and Threats:***

- The subgroup has low or inexisting participation to international, non-french speaking, meetings.
- The technology used for several projects is outdated (*e.g.*, DGGE).
- Funding is rather low.

▪ ***Recommendations:***

- The subgroup should increase the participation to international conferences.
- The subgroup should use or develop state-of-the-art technologies (*e.g.*, deep sequencing instead of DGGE).
- Raising fund from the European community, participating to the EU H2020 framework program have to be envisioned.

5 • Conduct of the visit

Visit date:

Start:	January 30th 2014 at 9:00 am
End:	January 30th 2014 at 5:00 pm

Visit site:	U 1047
Institution:	UFR Médecine
Address:	186 Chemin du Carreau de Lanes, 30908 Nîmes Cedex 2

Conduct or programme of visit:

AERES Scientific delegate: Ms Sophie de BENTZMANN

Expert committee: Mr Eric CASCALES (Chair), Ms Marie-Cécile PLOY (INSERM CSS7), Mr Tom COENYE, Mr Jean-Jacques LETESSON, Mr Philippe MOREILLON, Ms Astrid van der SAR

9:00-9:15 am	Presentation of AERES visit philosophy and of expert committee by the AERES scientific deputy
9:15-10:15 am	Presentation of the unit, past activities
10:15-11:00 am	Presentation of the unit, projects
11:00-11:15 am	Break
11:15-11:45 am	Meeting with technical staffs and non-permanents, and permanent researchers
11:50-12:10 pm	Meeting with the director
12:10-12:30 pm	Meeting with the supervising institutions and bodies
12:30-1:45 pm	Lunch
1:45-4:45 pm	Closed meeting of the committee
5:00 pm	End of the visit

6 • Supervising bodies' general comments

Université Montpellier 1

Instituts thématiques

Inserm

Institut national
de la santé et de la recherche médicale

Nimes, 2nd April 2014

We thank the AERES evaluation committee for their report and recommendations. We have carefully considered the comments made during the visit and in the report and have already initiated plans for implementation of their suggestions in our research and management strategies. We appreciate the positive comments about our overall output (publications and international meetings) and overall strategy, and we are extremely pleased to find that our new scientific focus adopted four years ago with the creation of our new unite, towards a more cellular microbiology and immunology approach is well appreciated.
We regret however to see that the written report concentrates on constructive criticism that seems to be aimed at helping us further improve some of the points that we believe are our strengths. The, sometimes contradictory, statements, that we will discuss point by point below, give a very negative feel to the report. The scientific quality and our exciting and innovative results that were presented in both the written report and during the visit are not mentioned in the report.

Specific points

1. Visibility

We are convinced that one of our strengths is our networking and national and international visibility. This is highlighted by the attraction of many (including foreign) PhD students, visitors and scientists from all over the world (at present we have almost 50% non-French lab members from 6 different nationalities), multiple invitations to speak at international meetings and workshops, organization of international meetings, participation in a European network and COST action etc. We therefore find it unfortunate that the report mentions at many occasions that we should improve our visibility, either in Montpellier, or at the international level. Although we do appreciate that differences exist between the three subgroups, and we will follow recommendations made by the committee to join more general meetings to enhance visibility at a more general level when possible, some of the comments seem in contradiction with the above average level of PhD students compared to groups in Montpellier (see below), the high numbers of visitors and foreign students, invitations at meetings etc.

Interaction with groups and visibility in Montpellier.

The report mentions that *"due to the isolation of the unit on the Nîmes campus in the Montpellier area, the interactions with other research units in Montpellier are rather limited."*
Although we are geographically separated from the main Montpellier campus, this has never been an obstacle for our local interactions. In fact, we have several scientific projects with groups in the Languedoc-Roussillon and Provence-Alpes-Côte-d'azur regions (Montpellier, Marseille, Marcoule and Nice), which may not have come out well during the visit, but are well-described in our report. This includes several shared PhD students financed by the foundation *Méditerranée Infection* on both fundamental and clinical projects. The clinical group works in close collaboration with clinicians and the microbiology laboratory at the CHU in Montpellier, as well as with other hospitals in the region and several projects in collaboration with URMITE in Marseille. They also have a very productive long standing collaboration with chemists at the Université Montpellier 2 which has been funded by ANR and EU FEDER grants. The fundamental groups have regular meetings, discussions and share tools with the groups in Montpellier working on intracellular pathogens (*Brucella*, *Coxiella*, *Salmonella*, Mycobacteria) and zebrafish (including, but not restricted to the Club Zebra) However our projects are often distinct and

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direct collaboration is not warranted. It is more logical and productive for us to establish collaborations with other groups throughout the world that offer expertise that is complementary to ours such as structural biologists in Lyon or proteome experts in Marcoule. In the past few years, we have applied for several joint projects with a group at the CPBS and two different groups at the IRD in Montpellier and with the CEA in Marcoule, unfortunately without positive outcome, and we are now applying for another joint PhD student project.
Further, the laboratory leader is part of the animation committee of the 'Interactions Host Microorganism' network that assembles groups in the Languedoc-Roussillon region working on different aspects of interaction from infectious disease to symbiosis in humans, animals, invertebrates and plants. This network organizes an annual meeting giving a platform for scientists and students in the region to present their work to a diverse audience. We were also members of the 'Montpellier Infectious Disease' network and gave presentations at several of its meetings. Our invitations and participation in other networks, including the G-RREMI (Groupe Régional de Recherche en Microbiologie des Interactions in Lyon/Grenoble), and the 'Groupe de Recherche Pseudomonas', also shows visibility at the National level.
The evaluation report suggested that *'maybe the unit should organize more regularly seminar series with invited speakers'*. We have been organizing seminars for several years; they are either held in Nîmes (an example is a recent seminar series of renowned Montpellier scientists at the midterm meeting of our MC training network) as well as seminars from several scientists from the USA, or co-hosted with a group in Montpellier. As the committee recommends, we will continue with this programme, and try to increase the number of seminars.
Finally one member of our unit is the co-leader of the Infectious Diseases group of the 'Pôle Rabelais', the new network that coordinates the teaching and research in Biology and Health in our University.

International

The report mentions that the international visibility of the clinical and to a lesser extent the *Burkholderia* research group should be improved, and we will follow the specific recommendations when possible (depending on financial and time constraints).
While it is true that the majority of the presentations of the clinical team have been in French meetings, we would like to add that over the last 5 years they have presented data at 9 international meetings over Europe. The clinical team also has a strong international network of collaborators throughout Europe and the USA and hosts visiting scientists and PhD students. The leader of the group was one of the members of a short list which recently created the ESCMID study group on *Staphylococci* (ESGS). This clearly demonstrates the visibility of the group.
The *Burkholderia* group is very active at the international level, and the lead scientist is well known in the type IV secretion field, the *Brucella* field, and *Burkholderia* community (in April 2014, we are hosting the 'International *Burkholderia cepacia* Working Group' meeting in Nîmes). Activity in the zebrafish disease field (participant in an ongoing European MC training network, and presentations by lab members at the annual international zebrafish disease model workshop), as well as an invitation to participate in a EU funded COST action leading to nomination as member of the Management Committee for France (as suppléant) in 2012, based on the development of the zebrafish model, show the international visibility also in this research area. The research group is indeed not strong in immunology, and recommendations made by the committee will be taken to heart.

2. Scientific project.

We are happy to see that the committee had no negative comments concerning the scientific quality of our projects. We do, however, agree with their comments that the *Brucella* project was unreasonably ambitious and does not have enough critical mass to be competitive on all of the aspects of the proposed project. Since our discussions on the day of the evaluation, we have taken their comments to heart and have redefined our priorities; we feel that this will

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allow us to be more productive. As suggested by the committee, we will re-focus on the areas for which we have the skills and the manpower, *ie* cellular microbiology of *Brucella*, with a focus on eukaryotic proteins involved and role of OMV. Also, the PI in this group, who has been developing their own research lines without any help since their arrival in the unit, is now in charge of a PhD student who's project will be developed in collaboration with a group in Marseille (Worldwide known for their expertise in *Brucella* cellular microbiology). This will strengthen the group of cell biology and will undoubtly lead to more publications in this field.

The committee's report suggests that "*The technology used for several projects is outdated (e.g., DGGE)*" is a weakness for the clinical project. We think that there has been a misunderstanding; although we presented data using DGGE, in our project we are developing the use of new technologies such as next generation sequencing in our metagenomic studies as well as culturomics and metabolomics. This will be done in collaboration with the platforms in Marseille (URMITE).

3 Publications

Although fundamental projects usually require much more experimental time, and thus in general are "less productive" in terms of numbers of publications than clinical research, the committee correctly pointed out the misbalance between the number of publications of the fundamental and clinical aspects of the project. The fundamental projects are only now starting to harvest the fruits of the new projects developed over the past years. Since the project was submitted to the university in September, the fundamental teams have 3 more papers published, have submitted a further three and are working on several others The clinical team have submitted a further 14 manuscripts (3 accepted, 3 in revision) and are working on several others for submission in the next few months.

4 PhD students

At several points throughout the report it is repeated that the number of PhD students is too low, giving a negative impression of our ability to attract students. We find these comments confusingly contradictory:

Although the report acknowledges that this is partly described to be due to the French system *"The number of PhD students in the unit is rather limited. This is however partly due to the French system which limits the number of students"*, the report also implies that this is related to limited visibility, and low involvement in the graduate school in Montpellier. *"The committee also encourages the unit to host more PhD students. This can be achieved by developing more connection with the University of Montpellier (higher involvement in the teaching activities, access to the Doctoral School council"*. The number of PhD students in our research unit is above average compared to other labs in Montpellier: This was actually acknowledged by the committee *'However, although this number seems limited, discussion with the representative of the doctoral school showed that the unit is doing well and that the number of PhD students is above average compared to other units belonging to the University of Montpellier'*. This clearly indicates that we are competitive with other research groups in Montpellier and also visible for the students that chose their projects based on a list of research topics.

We agree with the committee that involvement in the ED is important. That is why, in contrast to what is mentioned in the report ("*It is worthy to note that none of the unit members are part of the doctoral school council or participate in the selection committee for PhD fellowships"*), two members of the laboratory were members (one as subcommittee president) of the ED Doctoral Concours in 2011, and will continue to do so in the next years. However, this being said, this would not improve our chances of more PhD students through the ED, since the students chose their topic. As additional information, in 2011 our laboratory obtained two of the total 14 PhD grants for the whole of the ED.

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Limitations of the French system in number of PhD students, and the mode of acquisition of PhD students may indeed be low compared to other research laboratories abroad, and we appreciate the suggestions to attract foreign PhD students, which would help us to be more competitive at the international level. We do not agree with the comment that we are not attractive for such students because of low international visibility (*"The attractivity for external PhDs or post-doctoral fellows is very low (except visitors involved in collaborative projects) and one may expect to see more foreign young researchers joining the unit with an increased participation to international meetings and with an increased publication rate."*). The many international visitors including PhD students, for periods between 3-18 months in the different groups, are proof of our international visibility.
A small correction concerning the number of PhD students in 2015; one PhD student for the *Burkholderia* project, one for the *Brucella* project and 2 for the clinical project. At present we have 5 PhD students registered at UM1 and a student from Portugal on a long term visit. The committee commented that three PhDs defended in recent years was '*not overwhelming*'. It should be remembered that two of the scientists in the group have only recently obtained their HDR.

The report also suggested that we should improve our implication in the Masters Programme. Several members of the laboratory do participate in teaching of the Masters programme, and we also propose research projects for M1 students (we do not have funds to cover the Gratifications de Stage for M2 students). However, for safety reasons, we do not allow Masters students to work on *Brucella*. More importantly, one member of the Unite directs the BIOTIN specialty in the regional biology-health Masters programme and is also setting up an 'Innovation Week' for PhD students in the doctoral school in collaboration with INSERM-Transfert and the pole 'Entrepreneuriat-Emploie', and is contributing to different European Innovative training Networks. As a previous director of the Université de Nîmes, he is still the head of both the biology and biotechnology bachelor's degrees allowing the introduction of many students for training in the lab at an early stage of their education. It also opens the possibility of affecting an ATER position in the unit.

5 Funding

Our laboratory has a very strong record for its number of permanent scientists in attracting financial aid and participating in national and international programmes, including ANR, VLM, FRM, and European grants (Marie Curie ITN, Erasmus). The report pointed out the fact that our ANR funding has finished. Unfortunately the two ANR projects, and a Marie-Curie IIF grant we submitted recently were not successful. The reducing pool of ANR funds is a problem affecting the whole scientific community in France. We will continue with our requests. The report also suggested that we should pursue the EU as a funding source. We hope our participation in a European Marie Curie ITN that finances one PhD student, our implication in a European COST action (BM1003), and Erasmus programmes, will be in our advantage in our quest for financing in the Horizon 2020 programmes, depending on appropriate call topics being open. We will follow the advice of the committee to be more aggressive with this, including seeking financial support outside Europe.
We are very surprised that the report suggests that the clinical work is poorly funded, as we discussed this point with the committee. Although there is little funding through public funding such sources such as the ANR, ALL of the research projects that were described in the written document and during the site visit are fully funded through clinical research projects from the CHU Nîmes (PHRC and AOI), which has a very active policy in funding research and through industrial contracts.

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

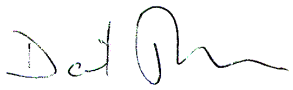
The report has under represented our interaction with the social, economic and cultural environment. Other than our strong interaction with the CHU, strong implication in teaching in

the University of Nimes, in the Montpellier 1 university, at the Ecole de l'ADN (one member of the team has founded this school with its network of 12 schools in Europe and Canada, and he is still his president) and local lycees, we would also like to point out the implication in the Eurobiomed Pole de Competitivite. One of the members of the Unite is general secretary, member of the board and responsible for the 'Emploi/Formation' group of the pole acting to professionalize student of our universities. This is providing an easy access to 250 members including 170 companies located in the south east of France and reinforce links between academics and private companies. This will also permit us, via the local CHU and the Nîmes and Montpellier 1 universities, to become an active partner of the DigiHealth biodiagnostic platform (ex CR2i) obtained by Eurobiomed from "Grand Emprunt" sourcing and also dedicated to infectiology.

7 Interaction within the laboratory

The committee has recommended that we strengthen the links between the fundamental and clinical sub-groups. *"The committee recommends that a global and more integrated strategy is defined for the evolution of the unit in the coming years. This is particularly important to strengthen the links between the fundamental and clinical researchers, not only by increasing the discussions between members (it is clear that this already happens) but by developing collaborative projects.*"

We agree with the committee that these interactions are one of the major strengths of our group. As pointed out by the committee, these connections do exist, as shown by several publications where scientists from different sub-groups are co-authors (*Microbes Infect.* 2013 ; *PLoS One.* 2012 ; *Int Urogynecol J*. 2011) with other publications in preparation. These interactions will be strengthened in future projects by more involvement of the fundamental scientists in the several aspects of the projects of the PhD students (*Staphylococcus*-cell interactions; effects of phage on *S. aureus* virulence and iron metabolism; effects of antibiotic resistance on virulence using zebrafish models). The clinical and fundamental scientist will also work together in several projects around the CNR *Brucella*.



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Montpellier, le 14 avril 2014

Référence : D. O'CALLAGHAN : S2PUR150008520 – Virulence bactérienne et maladies infectieuses - 04342321N

Messieurs,

Je tiens à remercier le comité de visite AERES pour la qualité de son rapport d'évaluation concernant l'unité U1047 « Virulence bactérienne et maladies infectieuses » dirigée par M. David O'Callaghan.

J'ai bien noté les remarques formulées par le comité de visite et je veillerai à ce que celles-ci soient prises en compte par le directeur de cette structure de recherche.

Vous trouverez ci-joint les commentaires du directeur de l'unité de recherche auxquels je n'ai rien à rajouter.

Je vous prie d'agréer, Messieurs, l'expression de mes salutations les plus respectueuses.

Philippe AUGE
Président
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