

URMITE - Unité de recherche sur les maladies infectieuses et tropicales émergentes

Rapport Hcéres

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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

Research unit on infectious and emerging tropical
diseases

From the

Université Aix-Marseille 2

CNRS

IRD

INSERM

DGA

March 2011



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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: Research unit on infectious and emerging tropical diseases

Requested label: UMR CNRS, UMR IRD, UMR_S INSERM

N° in the case of renewal:

Name of the director: M. Didier RAOULT

Members of the review committee

Committee chairman

M. Laurent Gutmann, Hôpital Européen Georges Pompidou, France

Sub-committee chairmen

M. David H. WALKER University of Texas Medical Branch, Galveston

M. Xavier NASSIF, Université Paris-Descartes, Paris, CNU representative

M. Ulrich DESSELBERGER, University of Cambridge, Cambridge, UK

M. François-Loïc COSSET, Ecole Normale Supérieure, Lyon, France

Committee members

M. David H. WALKER University of Texas Medical Branch, Galveston

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Observers

AERES scientific advisor

M. Nicolas GLAICHENHAUS

University, School and Research Organization representatives

Ms. Christine TUFFEREAU, INSERM

M. Benoit LOOTVOT, IRD

M. Stan TOMAVO, CNRS

M. Alain ENJALBERT, Université Aix-Marseille 2

M. Philippe MAUCLERT, Head of the Military Service

M. Laurent VIDAL, IRD



Report

1 • Introduction

• Date and execution of the visit

The visit was organized on March 14-15. After a 1 hour presentation by the head of the unit, the committee then split in several sub-committees:

- Sub-committee 1 reviewed teams 1, 4 and 10
- Sub-committee 2 reviewed teams 2, 3 and 9
- Sub-committee 3 reviewed teams 5, 6 and 7
- Sub-committee 4 reviewed teams 4, 11 and 12

Depending on the size of the team, oral presentations lasted between 60 and 30 minutes. The committee members also met University and research organization representative (for 45 minutes), PhD students and postdocs (for 45 minutes), engineers, technicians and administrative staff (for 45 minutes) and tenured researchers (for 45 minutes). At the end of the visit, the committee members met for 4 hours to write a preliminary version of the report.

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

The unit is localized at the Faculté de Médecine, 27 Bd Jean Moulin, in Marseille. The unit members are localized in four different sites including the Faculté de Medecine, the Faculté de Pharmacie, the hospital and the Pharo. The research unit is part of the RTRS Infectiopole and a founding member of the IHU. The budget in 2009 was 12 millions €. The research unit comprises several platforms including :

- A diagnosis platform ;
- An epidemiological clinical cohort of 700,000 individuals in Senegal ;
- A cell culture platform ;
- A microscopy and imaging platform ;
- A microbio-genomic platform (including transcriptomics, proteomics and bioinformatics) ;
- An insectarium.

• Management team

The head of the unit is Mr. Didier RAOULT. All engineers, technician and administrative personnel are platform members.



- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	39
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	8
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	11
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	52
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	
N6: Number of Ph.D. students (Form 2.7 of the application file)	
N7: Number of staff members with a HDR or a similar grade	35

2 • Overall appreciation on the research unit

- Summary

The committee were unanimous in considering that URMITE was a strong unit, but were less sure in knowing whether all teams were true teams, in particular teams 6, 7, and 10. In addition, team 9 appears to be more a support team.

- Strengths and opportunities

- The scientific output is outstanding;
- The unit is at the forefront for the identification and characterization of new emerging microbes;
- The unit is structured to optimise work towards the main aim of identifying and characterizing emerging microbes;
- The research unit has built a strong network over the years and was helped in this aim by their geographical location;
- The platforms use state-of-the-art technology;
- An integrated investigation for infectious diseases using 25000 diagnostic samples /year from France and abroad for the epidemiology and diagnostic of particular infectious diseases (Rickettsiae, Bartonella, Tropheryma whipplei, etc) and discovery of new infectious diseases;
- The unit has created multiple very well organized biobanks used to search new organisms and to test newly introduced diagnostic tests issued from their tranlational research and is equipped to establish additional biobanks as may be required for future research;
- The unit is able and flexible to create new teams (e.g. metagenomics, pathovirome, vector-transmitted bacterial diseases in Algeria);
- There is a strong capacity to develop a pipeline for students, from Master to Postdocs;
- The unit excels in the ability to culture newly discovered microbes.



- **Weaknesses and threats**

- While the unit in itself is well designed to work towards its scientific aims (new diseases, new species, new tests, novel phylogenetic analyses etc), the strength of the teams remains heterogeneous They should consider more fundamental hypothesis-driven questions based on their highly original data.

- **Recommendations**

- With the amount of genomic data that have been generated in the unit, the head of the unit should seriously consider investing in population biology;

- Bioinformatics should go deeper in connecting different databases.

- **Production results**

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	39
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	8
A3: Ratio of members who are active in research among staff members $[(A1 + A2)/(N1 + N2)]$	100%
A4: Number of HDR granted during the past 4 years	4
A5: Number of PhD degrees achieved during the past 4 years	50



3 • Specific comments

- **Appreciation on the results**

The quality and the number of the publications, scientific communications, thesis and other outputs: More than 250 publications have been published in excellent journals such as Nature, N Engl J Med, Lancet, Lancet Infectious Diseases, PLoS Negl Trop Dis, PLoS Genetics, Circulation and in good journals such as J Infect Dis, Clin Infect Dis, Emerg Infect Dis. In addition, a total of 50 PhD students have defended their thesis successfully (average duration : 3,5 years). Currently, the research unit is hosting 68 foreign students, mostly from southern countries.

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

The number and the reputation of the awards obtained by staff members, including invitations to international conferences and symposia: The head of the unit received the “Grand Prix INSERM” in 2010. Other unit members were granted the Young Investigator Award ESCMID in 2009, the Prix Jean Valade Jeune Chercheur in 2010, and the ERC Young Investigator Award. The members of the unit attend regularly and have also been invited to major congresses of microbiology and infectious diseases.

The ability to recruit high levels scientists, post-docs and students, and more particularly from abroad: During the past 5 years, a total of 50 students have obtained their PhD. On average, PhD students have spent 3.5 years in the research unit before defending their PhD. Currently, the research unit hosts 68 foreign students, most from Southern countries. All PhD students are funded and are enrolled in the Health Sciences PhD program of the University of Aix-Marseille 2. Fellowships are from different sources including the Ministry of Research, the Infectiopole, the PACA Regional Council, and foreign countries. Most of the foreign students are planning to go back to their home countries and to obtain a position there. All teams have regular (weekly) laboratory meetings. Students have the opportunity to present and discuss their data and to discuss papers published by others. Most students have had the possibility to attend scientific meetings, but very few attended meetings abroad. When leaving the laboratory, all PhD students have at least two first author publications and have participated in writing a review. The research unit also hosts a few postdoctoral fellows. Funding sources are diverse and include the CNRS, the infectiopole and foreign organizations.

The ability to raise funds, to successfully apply for competitive funding, and to participate to scientific and industrial : The annual research budget of the unit is 2.5 millions € including 5 ANR. They have been the incubator of a start up and have obtain recently an IHUfor infectious diseases.

The participation to international or national scientific networks, existence of stable collaborations with foreign partners: They have a very tight collaboration with IRD through members of their team and therefore develop many studies on infectious diseases (Rickettsiae, Whipple disease, etc) in foreign countries, particularly in Africa.

The concrete results of the research activity and socio-economic partnerships: This has led to the implantation of tools for the diagnoses of arthropode borne diseases in different African centers.

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

The relevance of the research unit organization, quality of the management and of the communication policy: Teams include more than 3 tenured researchers. All team leaders have a HDR and have been the corresponding author of at least 4 papers during the past 4 years.

The relevance of the initiatives aiming at the scientific resourcefulness and at the emergence of cutting edge projects: The Unit has a strong identity to search for new diseases especially those transmitted by arthropodes. They have large molecular scaling diagnostic tools to discover new infectious entities from clinical samples (encephalitis, endocarditis, etc) which will not be found by the standard approach.

The contribution of the research unit staff members to teaching and to the structuration of the research at the local level: At present, the research unit is linked to the University of Aix-Marseille 2, to CNRS, to IRD and to the military. For the next period, the research unit is seeking to be linked to INSERM. The 3 Universities in Marseille are going to



merge at the end of 2011. In this context, the universities have identified 8 scientific priorities, including 3 in biology of which one is microbiology. Therefore, the URMITE research unit will be fully supported by the merged universities. PhD students in the unit are enrolled in the Health Science PhD program of the University of Aix-Marseille 2. The research unit currently includes :

- 3 researchers and 5 engineers/technicians from CNRS. A new engineer position will be opened in 2012 ;
- 10 IRD engineers and researchers from the IRD. A new engineer position will be opened this year;
- 1 INSERM researcher from INSERM.

Regarding space, the unit has applied to the IHU call. If this application is successful, a new building will be constructed. Otherwise, the University is committed to allocate more laboratory space to the research unit.

Regarding the military, at present there are 4 research institutes in France including one in Marseille, one in Grenoble, one in Paris (Bretigny) and one in Toulon. There will be only one in the future at Bretigny, and the institutes in Grenoble, Toulon and Marseille will be closed. All the research will be done in Bretigny. Therefore, all the teams (team 8 and to a less extent team 5 and team 1) will move to this new area after 2013. The partnership will continue. An agreement will have to be signed between the military and the other institutions.

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

The existence, relevance and feasibility of a long term (4 years) scientific project: The project is highly feasible. It aims at linking clinical observations to new microbes and vectors. The researchers have large cohorts, receive and collect many samples (from humans, animals [mammals, birds, insects], and the environment) and own a well organized biobank. They have developed the technical knowledge to do all the diagnostic work using classical and advanced techniques. The project extends genomics, bioinformatics, and different animal models including an insectarium.

The originality and existence of cutting edge projects: The research unit scientific strategy is based on (1) emergence, (2) technology and (3) large access to human and animal samples. The researchers develop new diagnostic tools from cell cultures to serology, immuno-PCR to massive sequencing for diagnostic work, phylogenetic analyses and clinical pathophysiological collaborations. As a particular characteristic, the results of scientific projects have led members of the unit to shake established scientific systems, e.g. those of the classification of microbes and other forms of life.



4 • Appreciation team by team

- Team 1: Rickettsia and emerging pathogens
- Name of the team leader: M. Didier RAOULT
- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	
N6: Number of Ph.D. students (Form 2.7 of the application file)	
N7: Number of staff members with a HDR or a similar grade	3

- **Appreciation on the results**

The relevance and the originality of the research, the quality and the impact of the result: The leader of this team has created the URMITE. He has been among the rare researchers in France with an interest in arthropod borne diseases and has developed many tools to carry out and improve the diagnostic of these diseases. Another aim which has been achieved several times was to find new unidentified microbial species. These capacity to diagnose particular microbes has been extended to endocarditis, encephalitis and other pathology such as caused by *T. whipplei* that they have been the first to cultivate. They have also improved and made innovative contributions to the therapeutics against these agents.

The main accomplishments included:

- The national and international recognition of the National Reference Center for Rickettsioses and Emerging Zoonoses which is also WHO Collaborative Center on Rickettsiae and arthropod-borne bacteria. They discovered many new arthropod-associated bacteria associated with human and animal diseases.
- The new strategy for treatment of intracellular bacteria infections including new therapeutic approaches for *Tropheryma whipplei*. J Antimicrob Chemother 2008;61:968-9. New Engl J Med. 2007; 356:55-66. Nat Rev Gastroenterol Hepatol 2010;7:246-8.
- The research on *Tropheryma whipplei* and Whipple's disease. They were the first to culture of the organism in 2000 and have since used this capability to explore the epidemiology of *T. whipplei* which seems to be present in the stools and saliva. J Infect Dis 2008;197:880-7. Clin Infect Dis 2008;47:659-7. Emerg.Infect. Dis. 2009;15:922-4.



- The diagnostic for Infectious cardiology. This include serological, molecular, and histopathological assays to investigate specimens from patients suspected of having blood culture-negative endocarditis. Clin Infect Dis 2010;51:131-140. Lancet 2011. PLoS ONE 2010;28;5:e8939.

- The assessment of the digestive tract and emerging pathogens in Africa using approaches based on their knowledge on culture media and molecular biology.

The quality and the number of the publications, scientific communications, thesis and other outputs: The team members have published an impressive numbers of papers including 1 in Nature in 2008, 6 in *PLoS Negl. Trop. Dis.*, 8 in *N Engl J Med*.

A total of 15 students have obtained their PhD during the past 5 years.

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

The number and the reputation of the awards obtained by staff members, including invitations to international conferences and symposia: The team leader received the Grand Prix de l'INSERM in 2010. He has been invited to major conferences all over the world as a keynote speaker.

The ability to recruit high levels scientists, post-docs and students, and more particularly from abroad: Many student are recruited in the local univesity but also from southern countries.

The ability to raise funds, to successfully apply for competitive funding, and to participate to scientific and industrial clusters: excellent.

The participation to international or national scientific networks, existence of stable collaborations with *foreign partners*: Numerous collaborations exist nationally and abroad (US, Australia, UK, Africa).

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

The existence, relevance and feasibility of a long term (4 years) scientific project: The project is in direct continuation with the previous projects and there is no doubt that it will extend the knowlege on the theme.

During the next five years the team is planning :

- To search for novel diagnostic approaches: immunoproteomic; immuno-PCR, serological chips and development of new culture media (*C. burnetii* and *R. felis*);

- To search for new adjuvant therapies for intracellular bacteria infections: pentamidine , statins and omeprazole (*R. conorii*, *C. burnetii*, *Y. pestis*);

- To extend their knowledge on *Tropheryma whipplei* and Whipple's disease;

- To optimise culture techniques, continuing characterizing the clinical manifestations of pediatric diseases, to carry out research of hereditary specific immunodeficiencies;

- To search for biomarkers to better evaluate in clinical practice the prognostic of Infectious disease in cardiology and assess the role of statins in the prevention and the severity of endocarditis;

- To decipher the repertoire of possible etiologies of diarrhea in Senegal.

The originality and existence of cutting edge projects: This team has a major expertise to find new diseases and to use their technologies to develop new diagnostic tests. Taking advantage of their capability to cultivate and diagnose particular species, they will be able to describe the microbial causes of unusual infectious diseases.



- **Conclusion**

- Summary

This team is planning (1) to progress in the diagnostic of infectious diseases in general and discover new agents by improving known technologies and developing the most up-to-date technologies, and (2) to search for new therapies for difficult-to-treat intracellular diseases. The team and its specific research are outstanding.

- Strengths and opportunities

- The scientific output is outstanding;
- The team is a world leader in the diagnosis of infections with Rickettsiae and other arthropod-borne diseases;
- The team is both the national (CNR) and the WHO Collaborative Center for Rickettsiae (25,000 samples are collected every year);
- Very large networks of collaborations have been built over the years which will allow this team to discover new arthropod-borne diseases;
- Opportunity: The capacity to diagnose new pathogens that could be present in samples from patients suffering from endocarditis, and other diseases;
- The very active role played by this team in the training of foreign scientists and PhD students.

- Recommendations

- Keep going.



- Team 2: Tools for the detection, identification and characterization of emerging pathogens
- Name of the team leader: M. DRANCOURT
- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	3
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	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
N6: Number of Ph.D. students (Form 2.7 of the application file)		
N7: Number of staff members with a HDR or a similar grade	2	3

- **Appreciation on the results**

The relevance and the originality of the research, the quality and the impact of the result : The team developed an original research program that contributed to a better knowledge of (i) plague transmission and history (the team is a pioneer in the latter and leader in paleomicrobiology) and (ii) taxonomy/identification and ecology of mycobacteria.

Three themes have been studied in this team during the past 4 years:

- Theme 1 : Emerging and rememerging microorganisms : *Yersinia pestis*, *Mycobacterium*
- Theme 2 : Emerging organisms in complex human microbiota : *Planctomycetes*, *Archae*
- Theme 3 : Emerging pathogens in ancient specimens (paleomicrobiology) : *Bartonella*, *Rickettsia*, *Yersinia pestis*

Most significant discoveries made by the team during the past 4 years include :

- The demonstration that *Yersinia pestis* persists in the soil as a telluric organism (theme 1) (*Microbiology* 2008) ;
- The development of new tools for the identification/isolation and culture of *Mycobacteria* (theme 1) (*PLoS Negl. Trop. Dis.*, 2007, *Microbiology*, 2009). This work resulted in the identification of 8 new mycobacteria species;
- The demonstration that amoebias act as a Trojan horse for non-tuberculous *Mycobacteria* (theme 1);
- The demonstration that *Planctomycetes* are present in human stools (theme 2);
- The identification of a new type of *Archae* in human stools (theme 2);



- The identification of plague in mass grave in Europe (theme 3) (Emerg Infect Dis, 2007).

The quality and the number of the publications, scientific communications, thesis and other outputs : The team produced eighty papers, of which one-fourth was published in outstanding journals of infectious diseases/microbiology (Lancet Infect Dis, Genome Res, PLoS Pathog, PLoS Genetics, Emerg Infect Dis, Clin Infect Dis). The head of the team supervised 4 PhD students.

The quality and the stability of partnerships : The team collaborated with several international (Canadian and British), national and local partnerships.

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

The number and the reputation of the awards obtained by staff members, including invitations to international conferences and symposia : The team leader is deputy editor of Clinical Microbiology and Infection (since 2008) and member of the editorial board of Emerging Infectious Diseases (since 2006). He was invited as speaker at the 106th and 107th General Meeting of the American Society for Microbiology and at the 51st Interscience Conference on Antimicrobial Agents and Chemotherapy.

The ability to recruit high levels scientists, post-docs and students, and more particularly from abroad : One post-doctoral fellow (originated from the Imperial College, London) was recruited for the present project and PhD students supervised by the team leader were Algerian , Tunisian, Indian and Vietnamese.

The ability to raise funds, to successfully apply for competitive funding, and to participate to scientific and industrial clusters : The team leader coordinated two research programs from (i) the Ministry of Health, involving 17 teams and aiming to evaluate innovative technologies in medicine(2006; 1300 k€) and (ii) from the Ministry of Research, relative to emerging infectious diseases (ANR grant 2008 Boretic; 363 k€).

The concrete results of the research activity and socio-economic partnerships : Four patents (and 3 pending patents) concerning diagnostic tools resulted from the research activity, and one book covering paleomicrobiology was published by Springer in 2008.

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

The main objectives of the team for the next 4 years will be (1) to improve diagnosis for *Borrelia*, (2) to provide an integrative model for the transmission of plague, and (3) to find new archae and investigate their role in disease. Specific aims include :

- Theme 1 : Emerging and reemerging microorganisms :
 - Improve culture-based diagnosis for *Mycobacterium tuberculosis* ;
 - Investigate the role of cellulase in *Mycobacterium* and more specifically in their resistance to amoeba ;
 - Investigate the genomic plasticity of *Mycobacterium tuberculosis*, focusing on lateral gene transfer.
- Theme 2 : Emerging organisms in complex human microbiota :
 - Identify new *Archaea* species by improving culture conditions and by growing *Archaea* from intestinal and periodontal microbiota.
- Theme 3 : Emerging pathogens in ancient specimens paleomicrobiology:
 - Pursue the identification of *Yersinia pestis* in different soil samples.

The existence, relevance and feasibility of a long term (4 years) scientific project : The team will develop a wide research program the feasibility of which is questionable due to the relatively small size of the team (only 4 members,



of which 2 have clinical activities in odontology and ophtalmology, will be in charge for its implementation). A focused project should be considered by its leader.

The originality and existence of cutting edge projects The studies on genomic plasticity of mycobacteria and in vitro growth conditions of human planctomycetes and Archaea are original but also competitive at the international level.

- **Conclusion**

- Summary

The team will develop studies on the genomic diversity of some medically important bacterial groups and will set up new diagnostic tools from its cognitive research. Its good scientific productivity until now is a guarantee of success for the future.

- Strengths and opportunities

- The team is a leader in paleomicrobiology of infectious diseases;
- The team has contributed to a better knowledge of Mycobacteria in terms of taxonomy and to plague transmission, i.e. the team has demonstrated that body lice are also important agents for the transmission of plague;
- The team has developed tools for the development of new emerging pathogens;
- The relapsing fever project is very important as it is a neglected disease.

- Weaknesses and threats

- The number of projects is too large ;
- Threat: the work on Archaea is very competitive.

- Recommendations

- Focus on a more limited number of projects;
- Go one step further in the characterization of the new mycobacteria. The relapsing fever project is very important as it is a neglected disease.



- Team 3: Infections, gender et pregnancy
- Name of the team leader: M. Jean-Louis MÈGE and M. Eric GHIGO
- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	
N6: Number of Ph.D. students (Form 2.7 of the application file)	
N7: Number of staff members with a HDR or a similar grade	6

- **Appreciation on the results**

Because *Coxiella burnetii* and *Tropheryma whipplei* are very unusual organisms and the host responses in Q fever and Whipple's disease result in a broad range of clinical manifestations and duration of infection, the studies by this team have found interesting and unusual immune responses. These investigations are therefore unique in the field of immunology and may lead to better understanding of Whipple's disease and of the many faces of Q fever. The basic studies of infective endocarditis fit within the important focus of the overall unit on this disease. The mouse models of *Rickettsia prowazekii* offer for the first time the possibility to dissect the mechanisms of protective immunity and recrudescence.

The quality and the number of the publications, scientific communications, thesis and other outputs: The team produced 30 publications on their theme and participated in more than 40 collaborative publications. These included multiple primary publications in the highly respected journals such as *PLoS Pathog*, *J Infect Dis*, and *Infect Immun* as well as ten review articles in prestigious journals including the *J Immunol*. Six PhD theses were produced by the efforts of the team.

The quality and the stability of partnerships: The team's collaborations included cardiologists and immunologists as well as a number of excellent international collaborators.

During the past 4 years, the team has made significant discoveries including:

- The role of apoptosis in Q fever : *PLoS Pathog* 2008 and the role of IL-10 in chronic Q fever.
- The demonstration that *C. burnetii* repolarizes macrophages towards a M2 phenotype.
- The development of models for epidemic typhus and recrudescent typhus.
- The role of IL-16 in *T. whipplei* replication and phagosome biogenesis.



- Determination of a signature of infective endocarditis in the transcriptome of involved cardiac valves.
 - **Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners**

Information concerning the above-mentioned points was not clearly indicated in the application, except for partnership. The team will develop its research program with local and foreign (Slovakian, German and Italian) collaborators.

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

The scientific project will focus on the host response in infectious diseases using three complementary approaches: cell infection, tissue infection and translational medicine.

In a first project, the team will investigate how *C. burnetii* LPS interferes with phagosome maturation and macrophage maturation.

A second project deals with *Planaria* as a model to study bacterial infection [Rephrase].

A third project will deal with placental infection by *C. burnetii*. Placental cells will be prepared, and trophoblasts and macrophages will be purified. These cells will then be infected with *C. burnetii* and further analyzed by different techniques including gene expression analysis. The goal of this project is to address the following issues: which genes are commonly or differentially modulated in *B. abortus*- and *C. burnetii*-infected cells; which networks are modulated by each pathogen; and what is the role of the interactions between trophoblasts and macrophages in the infection profile and gene programs induced by each pathogen?

Another project will deal with translational medicine. The global aims are to provide effective answers to clinicians for their daily practice, to understand how intrinsic factors, such as gender and age, affect human infection, and to analyze the transcriptional response of patients with infectious diseases.

- **Conclusion**

- Summary

This is a strong team with substantial contributions to medical science including mechanistic studies. Their impact spans the spectrum from the laboratory to the diseases.

- Strengths and opportunities

- The team is a world leader in the investigation of immunity to Q fever;
- The team has developed an original and focused project on the cellular microbiology of *Coxiella*;
- Q fever in pregnancy is a very interesting topic, and the team is a leader in this field.

- Weaknesses and threats

- Genetic tools for *Coxiella* do not exist yet.

- Recommendations

- The project dealing with translational medicine requires clarification and maturation.
- The placental pathology of human Q fever in pregnancy needs to be evaluated and the target cells of infection identified in naturally occurring infections.



- Team 4: Emergent viruses and human pathologies
- Name of the team leader: M. Bernard LA SCOLA
- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	
N6: Number of Ph.D. students (Form 2.7 of the application file)	
N7: Number of staff members with a HDR or a similar grade	2

- **Appreciation on the results**

The research is of high quality and impact, in particular with regard to:

- Discovery of a parasite (virophage) of the giant mimivirus
- Discovery of a plethora of novel, uncharacterised giant viruses
- Use of Amoeba for cultivation of novel bacteria and viruses
- Discovery of Amoeba as a 'melting pot' in the emergence of chimeric microorganisms
- Use of Amoeba to characterise 'viral factories' of giant viruses
- Identification of bacteria and viruses by MALDI-TOF MS
- Flanking spacer sequencing for the molecular characterisation of bacteria

The group has produced publications of high quality in scientific journals of high impact (Nature, N Engl J Med, Proc Natl Acad Sci USA, J Virol, PLoS ONE).

The group has established high quality scientific partnerships.

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

During the last 4 years 5 MSc and 3 PhD projects were completed. At present, 3 PhD projects are ongoing.



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

The project includes:

- Search of emerging pathogens in the environment (water) by use of novel culture systems and metagenomics;
- Role of emerging microbial agents in human pneumonia and other disease syndromes by combined approaches including metagenomics;
- Development of tests using RNAs as specific bacterial viability markers;
- Investigation of serologic cross-reactivity of *F. tularensis* with by proteome analysis.

More specifically, the team members are planning:

- To use of Amoeba and other protozoa for cultivation/co-cultivation of environmental microbes and evaluation of their potential as human pathogens;
- To perform the complete genome sequencing of emerging microbial isolates;
- To study of microbial pathology in immunocompromised patients.

- **Conclusion**

- Summary

This team has been involved in major microbiological discoveries over the previous 4 years and has the capacity, the materials and all the tools to continue research at this level. The team will develop studies on the continuity of their expertise with development of new tools for evaluating drug resistance, new molecules and investigating mechanisms at molecular levels. Its applied research mostly in southern countries and integrated in long partnerships is a guarantee of success.

- Strengths and opportunities

- Strength: The team has discovered new pathogens, including giant viruses and virophages. These were extremely important discoveries that have opened new avenues of research in structural virology and the evolution of microbes; they have also led to strong international collaborations;
- Strength: The team has developed new cultivation methods (in Amoeba and other protozoa) to look for emerging viruses in various samples;
- Strength: The team leader has had a major impact in the development of this research and continues to be a driving force in the collaboration;
- Opportunity: The team has all the tools in hand to investigate the role of giant viruses in human pathologies;
- Opportunity : In association with other teams of the URMITE, this team has the tools to investigate gene transfer between viruses and bacteria in Amoeba and possible other protozoa.

- Weaknesses and threats

- Threat: The new microbes identified by the team may not be pathogens in humans;
- Threat: The involvement of plant viruses in human disease remains to be verified.

- Recommendations

- Find the balance between the discovery of new viruses and their relevance to human pathologies;



- Intensify research on the numerous recently discovered giant viruses;
- Consider Amoeba as host for experiments leading to direct evidence on the molecular evolution of microbes by lateral gene transfer.



- **Team 5: Surveillance and entomological approaches of emerging vectorial diseases**
- **Name of the team leader: M. Philippe PAROLA**
- **Staff members**

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	6
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	
N6: Number of Ph.D. students (Form 2.7 of the application file)	
N7: Number of staff members with a HDR or a similar grade	5

- **Appreciation on the results**

The team was led by Mr Philippe BROUQUI during 2008-2011 under the team name "Survey and Entomological Models of Ubiquitous and Tropical Emerging Vector-borne Diseases". The new team leader is a 39-year MD PhD. He is the director of the WHO Collaborative Center for Rickettsial Diseases and Other Arthropod-borne Bacterial Diseases.

The relevance and the originality of the research, the quality and the impact of the result: During the past 5 years, the team made a significant contribution to the knowledge of the geographical distribution of vector-borne Rickettsia infections. The team has studied vector-borne diseases in travelers including those of the large Comoros Island population in Marseille and in homeless persons in Marseilles. They have also investigated outbreaks and tick transmission models including one study that supports warm weather as a risk factor for increased likelihood of brown dog ticks feeding on humans and arboviruses.

The quality and the number of the publications, scientific communications, thesis and other outputs: These studies were published in 35 papers in specialized journals such as Emerg Infect Dis, Clin Microbiol Infect, Int J Infect Dis, Clin Microbiol Infect. The team also published 2 papers in PLoS Negl Trop Dis in 2008 and 2009. In addition, 4 PhD students have obtained their degree during the past 5 years.

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

The number and the reputation of the awards obtained by staff members, including invitations to international conferences and symposia: The new team leader made 13 international presentations.

The ability to raise funds, to successfully apply for competitive funding, and to participate to scientific and industrial clusters: The team participated in international research involving groups in Morocco, Algeria, and Gabon with numerous international collaborations in Europe, Africa, Asia, and the Caribbean.. The team leader is Director of



EuroTravNet, the ECDC Collaborative Network for Travel and Tropical Medicine. The research has expanded the knowledge of the distribution of infectious agents and the diseases that they cause.

- **Conclusion**

- Summary

This team has made significant contributions to knowledge of the etiology and epidemiology of global vector-borne infections. Its interests range from a variety of important vectors of bacterial, parasitic and viral agents such as sand-flies, ticks, lice and fleas to infectious diseases affecting different populations : hajj pilgrims, military personnel, travellers and specific important communities in Marseille (Comorians, homeless people). The team includes entomologists, travelers and military physicians, microbiologists, and pathologists in a very integrated structure.

- Strengths and opportunities

- Excellent surveillance programs;
- Premier group for the study of louse-borne infections;
- A unique focus on transmissible diseases in homeless persons;
- Outstanding program on tick-borne diseases ranging from an inventory of tick-associated agents in nature to experimental vector biology including the effect of warmer weather;
- The team leader is the director of the WHO Collaborative Center for Rickettsial Diseases and Other Arthropod-borne Bacterial Diseases.



- Team 6: Cystic fibrosis, microbiology and therapeutic approaches
- Name of the team leader: M. ROLAIN
- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	6
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	
N6: Number of Ph.D. students (Form 2.7 of the application file)	
N7: Number of staff members with a HDR or a similar grade	3

- **Appreciation on the results**

The relevance and the originality of the research, the quality and the impact of the result: The team have tested susceptibility and deciphered the resistance of particular organisms which are mainly those intracellular organisms studied in the unit. They have identified two epidemic strains, four additional strains that are resistant to multiple antimicrobial agents including colistin, and organisms that cause chronic colonization. Taking advantage of a large cohort of cystic fibrosis patients and of the URMITE platforms, they have established the responsibility of fastidious bacteria and have contributed to the identification of molecular mechanisms of antibiotic resistance in emerging pathogens in cystic fibrosis (CF) patients. They have tested some products (sterols) for their efficacy against intracellular pathogens .

The quality and the number of the publications, scientific communications, thesis and other outputs: Four PhD theses have been completed, and 21 papers have been published.

The quality and the stability of partnerships: The team works with Centre de Ressources et de Competences de la Mucoviscidose in Marseille which includes an adult center with 160 patients of whom 75 have received lung transplants. All are colonized with multidrug resistant bacteria. There is also a pediatric center with 110 patients and a prenatal diagnostic center.

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

The team leader has many national responsibilities. He is Member of MUCOMED network (CRCM de Nice, Giens, Marseille, Montpellier), Member of Administrative and Scientific Council of Société Française de la Mucoviscidose, Responsible of GRAM (groupe aérosols et mucoviscidose) and Président of Medical Council of Vaincre la Mucoviscidose (JCD 2005-2010).

The concrete results of the research activity and socio-economic partnerships: One patent application on synthesis of squalamine precursors and one license on the aminosteroids for topical application have been deposited.



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

The existence, relevance and feasibility of a long term (4 years) scientific project: During the next 5 years, the team plans to: (1) Carry on with the detection and the identification of new and/or emerging resistant pathogens in CF patients, (2) Evaluate the microbiotope in CF patients before and after treatment using high throughput sequencing, cultures and MALDI-TOF, (3) Carry out genomic analysis of epidemic and/or multiresistant bacterial strains and full genome sequence of *Inquilinus limosus* and *Pandoraea pulmonicola* to decipher the molecular mechanisms of resistance including colistin resistance, (4) Study the lateral gene transfer of antibiotic resistance encoding genes, (5) Develop new therapeutic approaches and new galenic forms using squalamine and aminosterols for the sterilization of inhalation devices and for potential drug delivery in lungs, (5) Investigate the dynamics of polymicrobial infections in CF patients.

The originality and existence of cutting edge projects: The study of the microbiotope in the CF patients could reveal interesting clues and influence therapeutic approaches.

- **Conclusion**

- Summary

The overall work presented in this project is good and important. This team is working on CF patients and will be able to use all the technology of the unit to find new microbial species or to evaluate the possible role of different species not known to be first line infectious agents. This part of the study is very likely to bring interesting results. As always, the therapeutic part of the study remain a challenge.

- Strengths and opportunities

- The team leader is a pharmacist and in a very good position to perform part of this project;
- The project fits well in the research unit and will benefit from the available methodology;
- Plenty of biological material is available from a large cohort of CF patients.

- Weaknesses and threats

- The search on new compounds could be promising as far as the sterilization of devices is concern. For the treatment of CF there is still a lot of work to be done.

- Recommendations

- Consider the possibility of screening more compounds to treat CF patients using nebulization and/or for sterilization of devices.



- **Team 7: Emergent severe respiratory infections and their assumption of responsibility**
- **Name of the team leader: M. Laurent PAPAZIAN**
- **Staff members**

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	
N6: Number of Ph.D. students (Form 2.7 of the application file)	
N7: Number of staff members with a HDR or a similar grade	5

- **Appreciation on the results**

A first goal of the team was to identify new causative agents of pneumonia. Human cytomegalovirus (HCMV) was found in patients with pneumonia several years ago. Further studies by this team demonstrated that other pathogens such as Tropheryma and mimiviruses were present in bronchoalveolar lavages (BALs) of patients with pneumonia. The team also demonstrated that(1) the presence of HCMV in BAL was associated with an longer stay in the ICU and (2) that the presence of HCMV in patients undergoing surgery for lung cancer was associated with an increased rate of complications.

A second goal of the team was to establish a new experimental pneumonia model. In a first study, rats were infected with Pseudomonas aeruginosa and developed a non-lethal respiratory disease. Rats were later treated with antibacterial drugs such as squalamine and one of its synthetic derivatives. Data showed reduced CFU. The team also investigate the effect of mechanical ventilation on endotoxemia in rabbits injected with LPS.

A third goal was to optimize pneumonia management, and more specifically to reduced ventilator-induced lung injury. In patients with severe acute respiratory distress syndrome (ARDS), the team showed that early administration of a neuromuscular blocking agent improved the adjusted 90-day survival and increased the time off the ventilator without increasing muscle weakness. This work was published in N Engl J Med in 2010. The team also investigated the possibility of using STATIN-VAP to manage patients with pneumonia.

During the past 5 years, the team published a large number of first and/or last-author papers in specialized journals such as Am J Respir Crit Care Med, Intensive Care Med, Crit Care Med, Anesthesiology and J Heart Lung Transplant. Of note, the team leader also published a first author paper in N Engl J Med in 2010.

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

The team has 3 Master students and two PhD students.

The team ranks well internationally and is among the top 6 laboratories doing clinical and experimental research on ventilation assisted pneumonia.



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

This group is taking the opportunity of the URMITE to better understand and decipher the role of infection and inflammation in ventilation assisted pneumonia. The long term project of this group is based on the results from the previous four years. In parallel, they will work in optimizing the management of respiratory infections.

- **Conclusion**

- Summary

In France, this team is a unique in associating experimental and clinical research in ventilation-assisted pneumonia. The team publishes well, has international recognition, and has numerous interactions and collaborations within URMITE. The team was therefore evaluated favorably by the committee.

- Strengths and opportunities

The team members are running the ICU, and therefore are the same who take samples from patients with ventilation assisted pneumonia (VAP) and other conditions of respiratory failure, and who analyze the samples for the presence of various pathogens.

This team has developed an experimental model that will allow them to better understand the relationship between severe pneumonia, lung injury and infection, as well as establish new therapeutic strategies.



- Team 8: Emerging tropical diseases
- Name of the team or project leader: M. PRADINES
- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	18
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	
N6: Number of Ph.D. students (Form 2.7 of the application file)	
N7: Number of staff members with a HDR or a similar grade	

- **Appreciation on the results**

Five major themes have been investigated during the past 4 years:

Theme 1: Evaluation of new antimalarial molecules and studies of drug resistance mechanisms, such as: reversion in vitro and in vivo of quinoeclin resistance by new synthetic molecules, optimisation of malaria prevention by cyclins and improvement of prophylaxy, evaluation of statins in cure and prevention of severe forms of paludism, in vitro analyses of the efficiency of groups of molecules against isolates of Plasmodium and reference clones.

Theme 2: Parasitological and vector proteomics and immuno-proteomics. Analyses by immuno-proteomics of the membrane antigens of infected hematies. Immuno-proteomics of arthropod salivary coupounds.

Theme 3: Development of field tests: Tetrapal (development of urinary test), MALADIA (development of new serological tools) and the use of remote sensing for transmission risks.

Theme 4: Epidemiological and genetic investigation of military personnel to vector-transmitted diseases.

Theme 5: Entomological evaluation of plasmodium transmission in urban areas with remote sensing technics and geographic information system.

Some significant discoveries made by the team during the past 4 years concerned new molecular markers linked to resistance to quinine (pfnhe1), the association between reversion to mefloquine resistance and a mutation on the codon 1042 of pfmdr1, and the use of two genes (pftetQ and pfmdt) as molecular markers for the following up of the sensitivity decrease to doxycycline.

The relevance and the originality of the research, the quality and the impact of the result: The team developed fundamental and applied research that has contributed to (1) the improvement of knowledge on drug resistance to malaria, (2) the development of new markers able to follow drug resistance in natural situations, (3) the evaluation of new molecules and (4) the follow up of epidemiological situations.



The quality and the number of the publications, scientific communications, thesis and other outputs: The team has produced significant publications in high standard journals of their domains of expertise (PLoS Negl Trop Dis, Am J Trop Med Hyg, Malar J, J Infect Dis, Emerg Infect Dis, J Med Chem), which contribute to their international recognition.

The quality and the stability of partnerships: The team collaborated intensively with several institutions in developing countries, but also with national and local partnerships.

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

The ability to recruit high levels scientists, post-docs and students, and more particularly from abroad: The team hosted students and scientists from southern countries. During the last 4 years 5 MSc and 3 PhD projects were completed. At present, 3 PhD projects are ongoing.

The ability to raise funds, to successfully apply for competitive funding, and to participate to scientific and industrial clusters: The team has been involved in several funded projects (national and international).

The participation to international or national scientific networks, existence of stable collaborations with foreign partners: Due to their experience in developing countries and COM-ROM, the team has established intense partnerships and trainings.

The concrete results of the research activity and socio-economic partnerships: The team is leader in the diagnosis and surveillance of drug-resistant malaria.

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

The main objectives of the team for the next 4 years will be (1) to develop rapid and accurate diagnostic tests, (2) to improve appropriate treatment of acute malarial infections, (3) to provide an active surveillance and to monitor temporal trends in parasite susceptibility of *P. falciparum* and *P. vivax*, (4) to identify molecular markers that predict resistance, (5) to develop new anti-malarial drugs. Five themes will be investigated:

- Theme 1: Improvement of laboratory diagnosis of malarial infections with development of alternative laboratory tools: rapid diagnostic test (RDT), PCR, and mass spectrometry;
- Theme 2: Surveillance of parasite populations with in vitro testing of drug resistance and molecular approaches of resistance mechanisms;
- Theme 3: Development of new antimalarial drugs with evaluation and investigation of mechanisms of action of new antimalaria drugs (cellular and ultrastructural approaches);
- Theme 4: Research on *P. vivax* in order to develop new antimicrobial in vitro tests, to identify molecular polymorphism of *P. vivax* isolates and biomarkers of latent infections;
- Theme 5: Mosquito-human interactions with the development of serological method based on antibody response against salivary proteins from vectors, completed by large-scale proteomic approaches on salivary glands' proteomes.

The existence, relevance and feasibility of a long term (4 years) scientific project: The Team has gained the expertise (see above) to conduct their scientific project without major risk.

The originality and existence of cutting edge projects: The integration of population genetics, markers of drug resistance in a spatially explicit epidemiological context using remote sensing technics and geographic information systems.



- **Conclusion**

- Summary

The team will develop studies on the continuity of their expertise with development of new tools for evaluating drug resistance, new molecules and investigating mechanisms at molecular levels. Its applied research mostly in south countries and integrated in long partnerships is a guarantee of success.

- Strengths and opportunities

- The team has developed an efficient international network for the diagnosis and surveillance of drug-resistant malaria;
- The team has discovered a new molecular marker for resistant to doxycyclin in malaria;
- The team is well aware that improving epidemiosurveillance needs to incorporate new tools and methods from immunology to teledetection.

- Weaknesses and threats

- Threat: the team will relocate in 2 years to Bretigny sur Orge near Paris;
- The former team leader recently left to head the Pasteur Institute in Madagascar;
- The project on the development of new method for diagnosis of malaria is more an attempt to improve technology than a research project.

- Recommendations

- To develop a strategy to explore new antimalaria drugs;
- To develop geographic information systems for the epidemiology of transmission and drug resistance.



- **Team 9: Bacterial genomics**
- **Name of the team leader: M. Pierre-Edouard FOURNIER**
- **Staff members**

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	
N6: Number of Ph.D. students (Form 2.7 of the application file)	
N7: Number of staff members with a HDR or a similar grade	1

The team currently includes 2 PhD students.

- **Appreciation on the results**

This a new team with a technology driven orientation. Therefore, this item is not applicable.

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

The number and the reputation of the awards obtained by staff members, including invitations to international conferences and symposia: The team leader is an MD, PhD. He has published 200 papers referenced in PubMed, and was invited as a speaker to 21 international meetings. Besides publishing papers on microbial genomic sequences in highly rated journals (PLoS One, Lancet Infect Dis, PLoS Genetics, Clin Microbiol Infect, BMC Genomics) the team leader has published widely in other areas of research. This team was part of the Network of excellence on pathogenomics.

The ability to recruit high levels scientists, post-docs and students, and more particularly from abroad: This team has only two permanent members. The head has also an appointment at the medical center as a Maitre de conférence and has clinical duties. This has team 2 PhD students, but no postdoctoral fellow.

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

During the next 5 years, the team members are planning to sequence the genomes of (1) several Rickettsia species, (2) several unusual bacteria such as colistin-resistant Actinobacter baumannii, (3) new species of Legionella. Furthermore, they plan: (4) to develop new specific molecular detection assays including multiplex PCR and microarrays, (5) to identify deficient metabolic pathways as clues to the development of new culture media, (6) to identify new antibiotic resistance mechanisms, and (7) to develop a genome-based taxonomy of Rickettsia species. To achieve their goals, the team members are planning to collaborate with several teams within the unit, including teams 1, 3, 6, 9 and 10, as well as with other teams in France (Evry) or abroad (Switzerland, USA).



- **Conclusion**

- Summary

This is a new team who will be providing very useful informations to the other teams of this unit.

- Strengths and opportunities

- The team leader has energy and a solid publication record.

- Weaknesses and threats

- The major weakness is that this team beside nucleotide (nt) sequencing does not really have a project and therefore appears to function more like a support team.

- Recommendations

- Nt sequencing should be followed by functional studies;
- The sequencing targets should be prioritized according to the results obtained by other teams, e.g. the results obtained by team 2 on Mycobacteria;
- Deeper approaches should be developed to expand on the information obtained from genome sequencing.



- Team 10: PathoViromes
- Name of the team leader: M. DESNUES
- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	
N6: Number of Ph.D. students (Form 2.7 of the application file)	
N7: Number of staff members with a HDR or a similar grade	0

The team leader is a young investigator who was recently awarded a starting ERC grant. Work supported by this grant contains an intensive program for the identification of new viruses via metagenomics and deep sequencing approaches on different pathologic or not pathologic samples.

- **Appreciation on the results**

The team leader has shown during her previous post-doctoral work that she can tackle new and difficult projects and take them to success, as demonstrated by the high-impact publications that she obtained. She has 12 publications in total, including 3 in Nature (in two of which she's first author or co-first author).

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

The team leader obtained an University Prize for her PhD work in microbial ecology in 2004 , a fellowship for young researchers from Marseille City 2008, an ERC Starting Grant in 2009, the Bronze medal of the CNRS in 2010, the Paoletti Prize in 2010.

The lab has two PhD students. The ability to raise funds is illustrated by winning an ERC starting grant in 2009.

The team leader has a good network of collaborations that should allow her to obtain the relevant samples and expertise. Contacts abroad are maintained from the time of her post-doctoral work.

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

The research proposed is at the forefront of virus discovery. The team will concentrate on the metagenomics effort in samples from pericarditis, encephalitis/meningitis, and pneumonia, in the context of the URMITE, and by maintaining contacts with other laboratories in France and abroad (USA). Preliminary data presented by the team leader already indicated important hits of viruses present in pericarditis samples.



- **Conclusion :**

- Summary

- This is a young team, which needs to be strongly supported.
 - The URMITE is the right environment to get the research done.

- Strengths and opportunities

- The team leader has an impressive record of publications, and has been a postdoctoral fellow in an internationally-recognized laboratory in the US;
 - The project is very focused;
 - Opportunity: The team has in hands a large number of samples (including controls) to look at new emerging viruses (encephalitis, pericarditis, and pneumonia).

- Weaknesses and threats

- In the search for viruses that are the cause of certain pathologies, there is always a risk of discovering new viruses which are not causative agents of the pathologies examined. Nevertheless, this study should contribute substantially to enlarging the viral repertoire, which is largely underdescribed.



- Team 11: Malaria and emergent infectious diseases in Africa
- Name of the team leader: M. Jean-François TRAPE
- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	
N6: Number of Ph.D. students (Form 2.7 of the application file)	
N7: Number of staff members with a HDR or a similar grade	1

- **Appreciation on the results**

The relevance and the originality of the research, the quality and the impact of the result: The program is based on a unique system of demographic and medical monitoring in Africa which includes more than 600 000 people living in 756 villages in Senegal. Keys results on the catastrophic emergence of drug resistance to malaria have been obtained with a direct impact on international recommendations to treat malaria.

The quality and the number of the publications, scientific communications, thesis and other outputs: From 2006 to 2010 more of 45 international publications including two publications in the Lancet in 2006 and numerous scientific communications are noted but no information on the thesis are given in the document.

The quality and the stability of partnerships: This program is based on a very long collaboration with Senegal and more recently with the Gates Foundation and the London School of Hygiene and Tropical Medicine.

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

The number and the reputation of the awards obtained by staff members, including invitations to international conferences and symposia: The team leader is an international reference in Malaria operational research. He received the « Prix IRD » and is a member of international panels (WHO, Gates Foundation, etc).

The ability to recruit high levels scientists, post-docs and students, and more particularly from abroad: A fantastic scientific programme has been realized since more than 20 years with a team of small size. The ability of recruitment is considered as being weak.

The ability to raise funds, to successfully apply for competitive funding, and to participate to scientific and industrial clusters: International grants from the Gates Foundation, the WHO, the Wellcome Trust, the EU, etc illustrate the capacity of the project leader to raise international funds.



The participation to international or national scientific networks, existence of stable collaborations with foreign partners: This is also a force of this team to set up an international partnership with the University of Dakar and the London School of Hygiene and Tropical Medicine.

The concrete results of the research activity and socio-economic partnerships: A very important result of the research is their direct impact on international recommendations to treat malaria. Another key result is the measure of the burden of tick-borne relapsing fever in Africa.

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

The existence, relevance and feasibility of a long term (4 years) scientific project: The demographic system of follow-up is an unique tool to provide original data on the strategies to control malaria. Thus, the project is really of great public health importance. Making use of the opportunities provided by this demographic cohort, research on others unknown causes of fever is being developed which is also important for public health strategies in this part of the world. Populations are follow-up since 1962; thus, we have no doubt regarding the productive continuation of the project during the next 4 years.

The existence and relevance of a policy for the allocation of resources: The funding for the next four years seems to be secured.

The originality and existence of cutting edge projects: The project is clearly multidisciplinary.

- **Conclusion**

This team is a leader in his field of research.

- Strengths and opportunities

- The project is very focused;
- The team has studied the epidemiology of malaria in two villages in Senegal for decades, and has made very important discoveries regarding malaria surveillance and control. Of note, these studies have been used by WHO to provide new guidelines for malaria control;
- Opportunity: The team is collaborating with medical and demographic platforms;
- The project to identify the cause of non-malaria fever in Senegal is original and well integrated.

- Weaknesses and threats

- Two of the 3 researchers of this team are born in 1948 and 1949. Therefore, the recruitment of new researchers should to be planned in good time and initiated.

- Recommendations

- The possibility of performing human genetic studies should be considered;
- A strategy of recruitment and training should be developed.



- Team 12: Vectorized bacterial diseases in Algeria
- Name of the team leader: M. BITAM
- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	---
N6: Number of Ph.D. students (Form 2.7 of the application file)	---
N7: Number of staff members with a HDR or a similar grade	3

- **Appreciation on the results**

The relevance and the originality of the research, the quality and the impact of the result : As head of a research unit at the Algiers' Pasteur Institute, the team leader - an expert of medical entomology at the Algerian Ministry of Health - is in charge to monitoring emerging and re-emerging arthropod- and rodent-borne diseases in the country. Beyond the special interest, his research (developped with experts in human infectious diseases) had undeniably a public health impact in Algeria.

The quality and the number of the publications, scientific communications, thesis and other outputs : The team leader produced 18 scientific articles (9 and 1 as first and last author, respectively), almost all being original papers, in peer-reviewed journals (Emerg Infect Dis, PLoS Negl Trop Dis, PLoS One, Am J Trop Med Hyg, Clin Microbiol and Infection). The team leader gave 7 lectures at international scientific meetings, and supervised 3 PhD students.

The quality and the stability of partnerships : The URMITE was the main partnership of the team leader during the past years. The head of the young team was also involved in a collaborative study with the Pasteur Institute networks (France, Madagascar and Vietnam) to evaluate dipsticks for Yersinia pestis antibodies detection in humans and reservoirs.

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

The ability to recruit high levels scientists, post-docs and students, and more particularly from abroad : The team is emerging and is still poorly attractive for post-docs and senior scientists; its IRD certification might facilitate foreign scientists recruitment.

The ability to raise funds, to successfully apply for competitive funding, and to participate to scientific and industrial clusters: The team leader is a partner of ANR grant 2008 (PHLEBO-MED; 46 k€) -coordinated by Dr Rémi CHARREL, "Émergence des pathologies virales", Université de la Méditerranée - and has recently applied for IRD certification.

The participation to international or national scientific networks, existence of stable collaborations with foreign partners: The team leader collaborates with different teams of the URMITE.

The concrete results of the research activity and socio-economic partnerships : The team leader improved the knowledge of the epidemiology of pathogenic microorganisms transmitted by arthropods in Algeria.



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

The team's projects aim at: (i) continuing work on an inventory of ticks, lice and fleas as potential vectors of infectious diseases in Algeria, (ii) studying arthropod biology and ecology regarding environmental (notably climatic) conditions, (iii) establishing the prevalence of arthropod infections due to *Borrelia*, *Rickettsia*, *Ehrlichia*, *Coxiella* and *Bartonella*, (iv) determining, through clinician and biologist networks, the incidence of borreliosis and rickettsiosis in humans living in Algeria, and (v) setting up a serum bank from infected patients. The team aims to become a reference center in its research field, not only for Algeria but also, in the short term, for other Maghreb countries.

The existence, relevance and feasibility of a long term (4 years) scientific project : This long-term project implicates a partnership between specialists in various field (entomology, medical microbiology, infectious illness, rodentology, ornithology, epidemiology, agronomy), giving credibility to its feasibility.

The originality and existence of cutting edge projects : The project will improve human public health in Algeria by making-up a network monitoring emergent/re-emergent infectious diseases in the country.

- **Conclusion**

- Summary

The goal of the project is to make an inventory of arthropods that transmit bacteria in Algeria and it fits well with the IRD missions. The project merits solid support.

- Strengths and opportunities

- This is a very focused project initiated and carried out by competent medical entomologists;
- The scientific output is very good;
- The team is specifically supported by the IRD to promote young research groups in the South.

- Weaknesses and threats

- The lack of postdoctoral fellows (at present).



Intitulé UR / équipe	C1	C2	C3	C4	Note globale
INFECTIOUS AND EMERGING TROPICAL DISEASES	A+	A+	A	A	A+
VECTORIZED BACTERIAL DISEASES IN ALGERIA [RAOULT-BITAM]	B	B	Non noté	A	B
PATHOVIROMES [RAOULT-DESNUES]	A+	NN	Non noté	A	A+
TOOLS FOR THE DETECTION, IDENTIFICATION AND CHARACTERIZATION OF EMERGING PATHOGENS [RAOULT-DRANCOURT]	A	A+	Non noté	A	A
BACTERIAL GENOMICS [RAOULT-FOURNIER]	Non noté	Non noté	Non noté	Non noté	Non noté
EMERGENT VIRUSES AND HUMAN PATHOLOGIES [RAOULT-LA SCOLA]	A	A+	Non noté	A	A
INFECTIONS, GENDER ET PREGNANCY [RAOULT-MEIGE-GHIGO]	A	A+	Non noté	A	A
EMERGENT SEVERE RESPIRATORY INFECTIONS AND THEIR ASSUMPTION OF RESPONSABILITY [RAOULT-PAPAZIAN]	A	A	Non noté	A	A
SURVEILLANCE AND ENTOMOLOGICAL APPROCHES OF EMERGING VECTORIAL DISEASES [RAOULT-PAROLA]	A	A	Non noté	A	A
EMERGING TROPICAL DISEASES [RAOULT-PRADINES]	A	A	Non noté	A	A
RICKETTSIES AND EMERGING PATHOGENS [RAOULT-RAOULT]	A+	A+	Non noté	A	A+
CYSTIC FIBROSIS, MICROBIOTE AND THERAPEUTIC [RAOULT-ROLAIN]	B	B	Non noté	A	B
MALARIA AND EMERGENT INFECTIOUS DISEASES IN AFRICA [RAOULT-TRAPE]	B	A	Non noté	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

Objet : Réponse au rapport d'évaluation - S2UR120001647 - URMITE - Unité de Recherche sur les maladies Infectieuses et tropicales Emergentes - 0131843H - de l'unité URMITE - Unité de Recherche sur les maladies Infectieuses et tropicales Emergentes.

Observations d'Aix-Marseille Université

Team 8: Emerging tropical diseases

Team leader: Bruno Pradines

Threat: the team will relocate in 2 years to Bretigny..

Only a part of the team will relocate in Bretigny. Six military researchers and technicians with tenured position will relocate in Laveran military hospital in Marseille. A laboratory of 350 m2 will be created in 2013 to relocate this team. The theme 1 (diagnosis), 2 (surveillance of parasite population with in vitro testing of drug resistance and molecular approaches of resistance mechanisms) and the theme 3 (development of new antimalarial drugs) will stay in Laveran military hospital in Marseille. The activity of associated laboratory of the National centre of malaria reference will stay in Marseille. B Pradines will be the leader of the team in Marseille, of the associated laboratory of the National centre of malaria reference and of the part of the team in Bretigny. B Pradines will spend 3 days in Marseille every week.

The former team leader recently left to head the Pasteur Institute in Madagascar.

The five themes, which will be investigated, are focused on fundamental and applied research in which the team is leader or has great experience. These themes are not the themes of predilection of the former leader team.

The recommendations will be taken in to consideration.

En accord avec les deux autres établissements d'Aix-Marseille

Le Président
de l'Université de la Méditerranée


Yvon BERLAND



Le Vice-président du Conseil Scientifique
de l'Université de la Méditerranée


Pierre CHIAPPETTA

