Département de microbiologie

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit:

Department of Microbiology

From the:

Institut Pasteur

October 2010

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

October 2010

Research Unit

Name of the research unit: Department of Microbiology

Requested labels: URA CNRS, Pasteur unit

N° in the case of renewal: URA 2172 for the CNRS superstructure

Name of the director: M. Patrick TRIEU-CUOT

Members of the review committee

Committee chairman

M. Alain FILLOUX, Imperial College, London, UK

Other committee members

Ms. Anna NORRBY-TEGLUND, Karolinska Institute, Stockholm, Sweden

M. Lynn ENQUIST, University of Princeton, USA

M. Werner GOEBEL, University of Würzburg, Germany

M. Friedrich GÖTZ, University of Tübingen, Germany

M. Richard MOXON, University of Oxford, John Radcliffe Hospital,UK

M. Oscar KUIPERS, University of Gröningen, The Netherlands

M. Mogens KILIAN, Aarhus University, Aarhus, Denmark

M. Agamemnon CARPOUSIS, University of Toulouse 3, France, CoNRS member

Observers

AERES scientific advisor

M. Nicolas GLAICHENHAUS

University, School and Research Organization representatives

M. Alain ISRAEL, Institut Pasteur

Report

1 • Introduction

- Date and execution of the visit

The committee visit occured on October 3-4 and took place at the Pasteur Institute in the Jacques Monod building. The visit was well organized and all committee members had the opportunity to prepare it carefully thanks to a rather comprehensive and detailed written document that they received well in advance. The document included a large volume describing past (2006-2010) and future activity of the URA2172 CNRS superstructure, and smaller volumes for each additional unit within the Microbiology department. The visit started with a welcome by the director of the Pasteur Institute and a short introduction by the head of the Microbiology department, and then the committee split in two sub-goups to evaluate each unit individually. Each team presented its past achievements and projects in about 45 minutes to 1h30, depending on the size of the unit. The committee members had the opportunity to ask questions and to develop a real discussion with the head and other members of the unit just after the presentations. On October 4, the committee members also met with technicians, PhD students, postdoctoral fellows, and other permanent scientists. The committee had also a private discussion with the head of the Microbiology department and the head of the URA2172 CNRS unit. Lastly, the committee members had a private meeting to summarize the visit and take decisison as for the evaluation of the individual units and the Microbiology department as a whole. On October 5th, the president of the scientific committee and few committee members attended the meeting of the Institut Pasteur scientific council. During this meeting, the president of the committee gave a first oral report about the evaluation, and each individual unit was also discussed by the other committee members. The sequence of events and organization of the visit was deemed excellent by all committee members.

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

The "Microbiology" Department was created in 2006 by merging the "Fundamental and Medical Microbiology" and "Microbial Pathogenesis" departments. It now includes 16 entities: 8 research units, 2 provisional units, 1 five-year group, 2 laboratories, and 3 collections of microorganisms. These entities are distributed in 7 buildings located on both sides of the Pasteur Institute campus (25 and 28 rue du Dr Roux). At the time of the evaluation, 6 out of the 16 Units/Laboratories of the Microbiology Department constitute the CNRS URA 2172, and the project is to include 5 additional entities in the future CNRS Unit tentatively designated “Functional and Molecular Microbiology” FMM) that will be headed by the same current director (see below specific evaluation of CNRS-URA2172).

Between 2006 and 2010, the department organization has remained essentially the same except for the emergence of few new entities, or rather new group leaders, which resulted from the retirement of senior PIs. The retirement of Michelle MOCK (Toxins and bacterial pathogenesis) has resulted in a transition with a new head of laboratory (Anaerobe Bacteria and Toxins), while another researcher of this unit has created an independent laboratory (Anaerobe pathogenesis) that will joined the URA2172 if this laboratory is confirmed. The retirement of Agnes LABIGNE has resulted in the division of the laboratory in 2 new units. One is a G5 group (Biology and Genetics of Bacterial Cell Wall) while the other is a provisional unit (Helicobacter pathogenesis). The retirement of Nicole TANDEAU DE MARSAC has left the Cyanobacteria unit more or less with only the Cyanobacteria collection and a very limited research activity. The retirement of Isabelle SAINT-GIRONS has resulted in the emergence of a new group leader and the transformation of the unit in a provisional unit (Biology of Spirochetes). Finally two other units have been closed whereas the scientists from these units have been reallocated to other units. In the end, the overall number of units has not been changed, but restructuration has occurred without the recruitment of scientists from outside the Institute.

In 2010, the department includes 31 DR (or equivalent), 30 CR (or equivalent), 19 research engineers, 42 technicians and 19 assistant technicians. The unit is also hosting a total of 59 PhD students and post-doctoral students all together. Finally 11.5 administrative staffs have also been listed. The total number of members in the unit in 2010 is 208 and has been stable since 2006.

The scientific activity of the department is obviously focussed on the Molecular biology of bacteria and in many cases bacterial pathogens are under study (*Yersinia, Clostridium, Helicobacter, Staphylococcus etc…*). The approaches are essentially based on basic molecular genetics or genomics, and address basic questions about bacterial metabolism or physiology and bacteria-host interactions. This is in the tradition of the Pasteur Institute to tackle questions relating to public health but it is also in the tradition of the Institute to have a deep understanding of fundamental aspects of the bacterial biology. A typical example is the work by the former Pasteur Institute famous scientist, Nobel Prize winner, Jacques Monod (after whom one of the building at Pasteur Institute is named) on the lactose operon. This work undoubtedly pioneered the study of bacterial metabolism and constitutes one of the most solid chapters in popular textbooks used by Microbiology students. The basic expertise in molecular genetics is complemented by other expertise such as structural biology and chemistry, infection and epidemiology, immunology or cell biology. These other expertises can be found within the department but are also frequently covered by internal collaborations at Pasteur Institute or external collaborations at the national and international levels. Within the URA2172 a number of themes are developed and include (i) protein traffic across bacterial membranes, cell surface and cell wall components (ii) bacterial biofilm, (iii) control of gene expression, (iv) metabolism and acquisition of nutriments, (v) genomic, evolution and epidemiology. The studies may be targeted at establishing purely fundamental concepts in bacterial physiology. In other cases the study are pushed further to understand how these mechanisms impact the interaction between a bacterial pathogen and its host. Studying the molecular mechanisms of bacterial virulence cannot be considered a minor activity of the department since several research entities are clearly involved in the study of bacterial infectious diseases and host a National Reference Center. That is particularly true when working on pathogens such as *Staphylococci and Streptococci, Yersinia, Helicobacter pylori, Leptospira or Clostridium*. In this context most of these units have implemented the use of animal models or established strong collaboration with clinicians or the external foreign laboratories belonging to the international Pasteur network. Outside of the URA2172, the other units constituting the Microbiology department have rather unique expertise. One unit is famous for the work on antimicrobials, another for the work on extremophiles archeae and their viruses, a third one has expertise in the characterization of bacterial toxins.

- Management team

The head of the Microbiology Department (Patrick TRIEU-CUOT) is also the head of the unit Biology of Gram-positive Pathogens. He took over the Department direction in 2009 from Patrick FORTERRE, who is also head of the unit Molecular Biology of Gene in Extremophiles. The role of the head of department at Pasteur Institute seems rather restricted, since the institute has an independent scientific council through which most of the key decisions are going. Therefore the head of Department essentially coordinates the scientific animation and proposes new strategies of scientific development to the scientific director. The head of department is now associated with a deputy director (Jean Marc GHIGO), who is also the head of the unit Genetics of Biofilms. In terms of scientific animation one of the major event in the year is the organisation of the “Journées du department de Microbiology”.

- Staff members

	Future
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)	61
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	61
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 2.8 of the application file)	
N7: Number of staff members with a HDR or a similar grade	

2 • Overall appreciation on the Department

The quality of the science in the Microbiology department, as compared to the rest of the world, is average to above average with some exceptional groups.

The scientific committee considers that

- It is a solid and good grouping of laboratories with international visibility and competitiveness,

- Several of the groups have high publication profile with several papers in general journals such as PNAS (12), EMBO Journal (4), Journal of Biological Chemistry (16) or PLoS Pathogens (10), but more occasionally in Journals like Nature journals (6), Nature Reviews (4), Lancet (1), PLoS Biology (1), PLoS Medicine (1) or Cell journals (2). Naturally, most of the publications go in the best journals of the Microbiology category, Molecular Microbiology (22), Infection and Immunity (22), Journal of Bacteriology (39), Antimicrobial Agents and Chemotherapy (22), Cellular Microbiology (9) or Applied and environmental biology (18). Importantly 60% of these publications are involving international collaboration. The number of the publications has increased over the years from 84 in 2006 to 113 in 2009. Of note, 62% of these publications are in the top 25% journals of the category.

The scientific committee found that the Microbiology department fulfils the mission expected from the Pasteur Institute by

- Delivering excellent Science on fundamental aspects of the molecular biology of bacteria or the virulence of important extracellular pathogens.

- Demonstrating a good balance between fundamental aspects and a more pronounced clinical orientation or study of bacteria-host interaction.

- Being very much complementary with other department at the Pasteur Institute involved in the study of intracellular pathogens with a strong focus on the interaction with the host (Department of Cellular Biology and Infection).

The scientific committee observed that several units developing top quality research does not show guarantee for sustainability, though the research theme should certainly be maintained within the department. This is the case for those units with ageing charismatic group leader for whom no obvious successors have been identified.

- Most striking example are the units "Molecular Genetics" and "Bacterial Membranes". The heads of these two units pioneered their field and dominated this research area for more than 25 years. In the former unit there are numbers of younger scientists but none of them is stepping forward to take on the lead. In the later the situation is more critical since none of the scientists seem to be in a position to take over once the leader will retire.

- Another unit "Antibacterial Agents" is at the end of a cycle and the PI in charge cannot be replaced internally if the Department wants to keep the same international visibility in this research area. Be this unit later on reorganized and the theme kept within the Department, it may be an opportunity to consider reorientation of the research by using more innovative and original approaches.

- The unit "Anaerobe Bacteria and Toxins" is also headed by an ageing scientist. The theme on toxin research has long been associated with the department and this area was shared with the symbolic unit headed by Michelle Mock, which is now closed. The future of this unit is thus questionable since on the one hand, no obvious successor has emerged from within the unit and on the other hand new units developing activity on clostridia and toxins have been created and are emerging from the previous Mock unit

- The unit "Molecular Biology of Gene in Extremophiles" performs original and high quality research and has an ageing leader. There are young researchers in this unit and in particular a scientist who is a brilliant evolutionary biologist. Though there is still time to think about the future of this unit it should be considered as quick as possible to avoid problems that are obvious in other ageing units.

The scientific committee identified units in which the leader has established his/her scientific niche and are now cruising to be among the best laboratories within the department. That is clearly the case for the unit on "Yersinia" and "Genetics of Biofilms". These two units are striking examples of laboratories, in which the leader has yet a long career to come, and which may guarantee the future identity and visibility of the Microbiology Department.

The committee also identified that in some cases restructuration combined with redistribution of staff coming from other units that were closed, slightly dampened the overall scientific visibility of the restructured unit. That is the case of the unit on "Biology of Gram-positive bacterial pathogens". The activity of this unit is excellent and the head of the unit can count on very good and promising young scientists. This is also one of the nicest examples of a unit with a very good balance between fundamental and clinically oriented research. Nevertheless, the restructuration and recent association of two subgroups on "Streptomyces" and ""Nosocomial infections" does not particularly contribute to increase the international visibility of this unit.

The scientific committee recognizes that some units are still on the move and it is not always obvious to predict whether their development will take them to the top Science quality expected in the Department.

- The unit entitled "Biology and Genetics of Bacterial Cell Wall" results from the closure of the previous unit headed by Agnes Labigne and is directed by a promising young scientist. He established his own scientific niche and received important awards such as ERC starting grant and INSERM-Avenir programme. This unit is a G5 group and undoubtedly promised to a brilliant future.

- The unit "Helicobacter pathogenesis" is also a recent spin off from the previous Agnes Labigne unit. The team leader has done a very good job in redefining the orientation of the unit and again has identified a niche where she can acquire international visibility. Be this unit encouraged and further supported, it could be the demonstration that anticipating retirement of ageing PI could be a path to success.

- The unit "Spirochaetes" is also headed by a young and promising scientist. The difficulty of manipulating these microorganisms slowed down a quick progress and the identification of cutting edge research area. However, the tools are now in place and be the study of these pathogens considered an important research direction for the Department, the future development of the unit should be supported.

- Two new units have emerged from the closure of Michelle Mock unit. These are "Toxins and Bacterial Pathogenesis" and "Anaerobe pathogenesis". The former seems to be the direct spin off from Michelle Mock's unit and the new leader will need to show a potential for innovation and originality in a research field dominated by M. Mock in the past years. The later will concentrate the work on *Clostridium* and has obviously succeeded in creating a new dynamic by being joined by other permanent scientists who are giving a real momentum to this young unit.

The scientific committee has had also a careful evaluation of the three collections, namely "CIP", "Cyanobacteria Collection" and "Fungi Culture Collection". Although the committee considers these collections as valuable tools and resources for the international Microbiology community, their localisation within the department or within the Pasteur Institute is questionable. For these units the main mission appears to distribute the strains, and only very little original research is conducted, though the heads of "CIP" and "Cyanobacteria collection" have likely done their best to develop some. However, and more generally, the committee did not find compelling arguments for the Pasteur Institute to remain the host of these collections and recommended to identify alternative hosts.

- In conclusion, no major problems were identified and overall the scientific quality and production of the department is excellent.

- However, the committee did see that there are many common issues of an ageing department arising (mean 54 years old). In other words, how is the Department going to make sure that the most brilliant and charismatic leaders be replaced, knowing that internal promotion will not be sufficient to keep the high international profile. Identification of new leaders is not easy and in several cases the "junior" group members are in their late 50's and their own retirement is also not far away. Nevertheless, young promising scientists do exist, some of them have already been promoted as head of units others are still under the umbrella of their unit heads and should be followed carefully. Two very good examples are in the "Molecular Biology of Gene in Extremophiles" and "Biology of Gram-positive bacterial pathogens".

- The choice of the bacterial pathogens under study in the different units sounds appropriate and they all are of public health importance. Anthrax study might be too limited and broadening to related pathogen such B*acillus cereus* is encouraged. Overall, the balance between public health and fundamental research is as it should be.

- The scientific committee would like to highlight that few methodological requirements should be carefully considered. In particular, and because that is something that is under study in several units, how the Department is going to address the needs for fine structural chemistry of carbohydrates. Also, further development of microscopic facilities, single cell analysis and micro-fluidics should also be evaluated carefully. The committee also recognizes the new developments in histopathology and use of animal models.

- The teaching load across the department does not seem very high. Only 4 staff members have teaching duties though most of the staff contributes to teaching. It is organized based on a rotation, and one unit at a time is in charge of the course and practical for "General Microbiology" and "Medical Bacteriology".

- The units in the department are spread on 2 sites and relocation or refurbishment of the laboratories is still going on. This is a good thing and can only improve the working conditions and positively impact the quality of the production and the implementation of appropriate facilities.

- Lastly, and despite they are valuable resources for Microbiologists, the committee cannot recommend the collections be kept within the department.

2 • Overall appreciation on the URA 2172 CNRS superstructure

• Summary

Most of the scientific activity of the URA2172 could be found summarized in the description of the Microbiology Department (above) or in the individual units (below). Briefly, the URA regroups units addressing questions about bacterial cell surfaces, gene transcription in bacteria, physiology and bacterial life-styles and where appropriate develops cellular ad animal studies to address the pathogenesic side of bacteria. Until now the URA2172 was called « Genetcis and Mbiochemistyry of Microorganisms » but in the next mandate (starting January 2012) it will become « Functional and Molecular Microbiology » (or FMM). The new URA will group 5 of the previous URA units, « Molecular genetics and transcriptional regulation » (or E1), « Biology of Gram-positive bacterial pathogens » (E2), « Bacterial membranes » (E3), »Genetics of Biofilms » (E4), and « Cyanobacteria collection » (E5). A further 5 units will join the FMM, « Yersinia » (E9), « Genetics and Biochemistry of Cell Walls » (E10), « Helicobacter pathogenesis » (E11), « Spirochaete Biology » (E12) and « Pathogenesis of bacyterial anaerobes ».

• Strenghts and opportunities

- Very good publication track record and international profile.

- The head of the URA is an highly cited researcher who largely contributed to the disseminatation of science within the international scientific community.

- The URA is hosting units whose leader range from the promising young investigator to the ageing star, and including leaders reaching the peak of their career.

- Excellent synergy between the themes developed by the different units.

• Weaknesses and threats

- Two of the charismatic leaders (E1) and (E3) are ageing and the future of their unit should be considered with care.

- Modest financial contribution from the CNRS.

- The unit « Cyanobacteria collection » is not providing a significant research input and cannot be considered as an entity of the URA.

• Recommendations

The scientific committee considered that the URA, which represents more than half of the Microbiology Department, is a major player. It has an international profile by the levels of publications and by the ability to disseminate Science through conferences and congress orgnaization. It includes most of the promising young units, which will be the future of the Department. These young units should be supported and encouraged to reach the international visibility that has been acquired by other charismatic leaders. At the same time those charismatic leaders should take position quickly and make consistent suggestions on how to make sure that historical and symbolic themes within the unit will not get lost because of the lack of credible successors. At the exception of the unit “Cyanobacteria collection” the scientific committee will thus recommend that the next URA be created according to the proposed organization chart.

- Production results

(cf. http://www.aeres-evaluation.fr/IMG/pdf/Criteres_Identification_Ensgts-Chercheurs.pdf)

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	
A4: Number of HDR granted during the past 4 years (Form 2.10 of the application file)	
A5: Number of PhD granted during the past 4 years (Form 2.9 of the application file)	

3 • Specific comments of the URA 2172 superstructure

- Appreciation on the results

Relevant comments are to be found in the description of the Microbiology department (above) and the evaluation of the individual units (below).

Briefly the concept of the URA is very attractive. Most essentially the themes considered are bacterial cell surfaces, gene transcription in bacteria, physiology and bacterial life-styles.

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

Relevant comments are to be found in the description of the Microbiology department (above) and the evaluation of the individual units (below).

Some of the team leaders are real pioneers in their research field and are at the peak of their career. Others have established an entire new research field and are amongst the most visible scientists in their research area. New investigators are emerging and are very promising young scientists.

The head of the URA has demonstrated an outstanding contribution to the dissemination of knowledge both by being invited to major international conferences (48 since 2006 including Gordon Conference, ASM etc…), but by being himself a major organizer of key conferences in his field (EMBO Summer school on membranes in Cargese, EMBO conference on Protein traffic in Sainte Maxime-2008). He has also be the senior editor for Molecular Microbiology and the chairman of EMBO Long-term fellowships committee.

- Appreciation on the management and life of the research unit

Relevant comments are to be found in the description of the Microbiology department (above) and the evaluation of the individual units (below).

This URA is a homogeneous grouping of units with complementary and synergic expertise, which provide an added value to the whole.

- Appreciation on the scientific strategy and the project

Relevant comments are to be found in the description of the Microbiology department (above) and the evaluation of the individual units (below). The most important threat concerns the ageing leaders that may not be replaced on time and therefore some of the research themes may lose a lot in terms of international profile.

4 • Appreciation team by team (URA 2172)

Title of the team : Biology and Genetics of Bacterial Cell Wall (G5 unit)

NHame of the team or project leader: M. Ivo GOMPERTS-BONECA

- Staff members

	Future
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)	2
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2
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 2.8 of the application file)	
N7: Number of staff members with a HDR or a similar grade	2

This is a G5 Junior group created in January 2008 and the mandate is thus due to terminate by the end of 2012. This group will then postulate to be one unit of the CNRS superstructure (URA2172), which will include a total of 10 units. The team leader (38 year-old, HDR in 2010, Chargé INSERM), previously worked in Prof. Agnes Labigne unit, "Pathogenesis of mucosal bacteria", which has since closed. Another permanent scientist (45 year-old, HDR in 2006, Chargé IP) joined the team leader just after the creation of the G5 group. The group is small, well equilibrated, with two PIs, 2 technicians, 2 PhDs and 2 Post docs. The two PhD students are about to complete their thesis. One of the two post-doctoral students is entirely devoted to the structural biology aspect of the project. The team leader wishes to enlarge the size of his group and at least one M2 student and an additional Post doc will be recruited.

Although none of the PI has compulsory teaching duties, they do so by delivering lectures on subject related to their research area to PhD and Master students.

In March 2009, the group moved in a completely renewed building with laboratories specifically adapted to the current needs (class 2 pathogens, solvents, etc…)

- Appreciation on the results

The team leader has an excellent expertise in the field of cell wall metabolism and peptidoglycan synthesis. He has a very good track record of publication (h21 for 34 publications), and is a very promising young scientist. The other permanent scientist has also a good track record (h17 for 33 publications) and an expertise in *Leptospira* LPS, TLR and Nod receptors, cytokines and inflammation, in vivo models of infection and immunology. Both PIs are thus forming a tandem with excellent complementary expertise and with leadership in their area. They share common research interest, which gives the overall project an excellent integrated aspect.

They published 9 papers during the period 2008-2010 and 3 reviews. To be highlighted are a Nature Immunology and a Nature paper (co-authored by the two PIs), though they are not the main authors (D. Philpott and G. Eberl, respectively). Among these publications, two major authorships have been obtained over the period, in

Applied Environmental Microbiology (2008, IF: 3,7) and Journal of Immunology (2009, IF: 5,7). This is very likely to improve massively in the coming years since the two PIs have not been in a steady situation for a long period of time.

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

The two PIs, but particularly the group leader, are invited to international conferences (for example the Annual SGM meeting in 2009) and seminar series.

The team leader has received awards and honours such as Prix Jacques Monod (2002), INSERM Avenir (2007) and ERC starting grant (2007).

The funding is a strength of the group. It includes an ERC starting grant to the team leader (1.65 M€ for 5 years), Avenir Programme (60k€/year), 2 ANRs (one for each PI) and some others. A collaboration with Danone is also reported (2008, 60k€ and a technician), which shows linked with industrial partners. Finally, the group leader holds two patents on intestinal homeostasis.

Various collaborative projects are ongoing which involves the Nod and TLR expertise. One example concerns the *Listeria/Shigella* autophagy process, which appeared dependent on Nod1, Nod2 and the autophagy protein ATG16L-1 (D. Philpott, University Toronto). The structural biology of Nod proteins alone or in complex with PG and ATG16L-1 is also proposed. Another side project is to study role of the *Yersinia* lysozyme inhibitor Ivy (F. Sebbane; Lille). Other collaborators are Fredric Veyrier (Mc Gill, Canada; invasive bacteria) Alain Vandewalle (Hopital Bichat, innate immune response) or Andrea Dessen (Grenoble, structure and inhibitors).

- Appreciation on the scientific strategy and the project

The activity is very broad and addresses many aspects of peptidoglycan (PG) and cell wall metabolism, including bacterial shape, antibiotic resistance host-bacterium interaction and the PG dialogue with the host immune system. It uses several model micro-organism including *Helicobacter pylori* and *Neisseria meningitidis*, but also *Leptospira*, *Yersinia* or *E. coli*, and involves *in vivo* studies in mice models. The project is primarily basic Science but is also directed towards applied medical approaches.

One part of the project on peptidoglycan metabolism and assembly takes *Helicobacter* pylori as model since it has a minimal set of genes involved in this process. Two new lytic transglycosylases (Slt and MltD) with new physiological role in relation with flagellar motility have been identified. The group identified a Slt inhibitor (Bulgecin A), which is indicative that the long-term goal is to identify therapeutic targets and new antimicrobials. The group also identified a novel interaction between EnvC/MreC (morphogenic protein) and PBP2. They showed that altering the stability of this complex kills H. pylori in vitro and will thus target this interaction in the search of novel antimicrobials. The main perspective is thus to pursue the biochemistry and structural biology of transglycosylases and search for inhibitors with various specificities. Reconstituting the *H. pylori* PG machine in *Neisseria* and investigate how it could affect the shape is another original and innovative approach in synthetic biology.

The other part of the project is addressing the host response. It appears more diverse and less integrated. It largely uses Leptospira as a model bacterium. It involves several sub-projects such as (i) Nod1-dependent signalling and IL8 secretion in response to various source of PG (Newborn and axenix mice infection model, hnod1 and hIL8 transgenic mice; bone marrow-derived macrophages from TLR, Nod and Nalp3-deficient mice); (ii) Specificity of recognition between Leptospira PG and Nod proteins; (iii) characterization of transglycosylase and amidase from Leptospira to understand subtle modification in *Leptospira* PG structure; (iv) use of a model of kidney fibrosis in mice induced by *Leptospira*, study the role of LPS or PG in the process and the TLR-independent response (tlr2/tlr4 mice model to reproduce the acute human disease); (v) Pharmacodynamics of PG distribution *in vivo*.

- Conclusion :

– Summary

This G5 junior group is an excellent combination of expertise between two PIs who already published together. The project is dedicated to the study of bacterial cell wall metabolism and understanding the host response to PG or LPS. The projects are diverse but based on original and novel data. It involves the identification of new transglycosylases in various bacterial species, as well as the characterization of their role and structure. These proteins are also selected targets for the design of new antimicrobials. The other aspect of the project dissects the inflammatory response to LPS and PG, using a variety of transgenic mice and cell lines, for which a clear expertise has been demonstrated.

– Strengths and opportunities

- The team leader has a real leadership, a rising international visibility and is doing excellent science

- Excellent funding record

- Very good publication track record

- Excellent expertise with animal models (own breeding, license and training).

- The complementary expertise of the two PIs is a major strength in this unit.

– Weaknesses and threats

- No genetic tools are currently available in the Leptospira model

- Collaborative aspects with other units working on Helicobacter should be highlighted.

- The route of infection that is used to infect mice with Leptospira is not physiological. Currently IP but shkin model will be more relevant.

- As other groups at the Pasteur Institute, this team needs to have access to carbohydrate fine structural analysis plateform.

- There is a risk of too much diversity in the projects, in particular the aspects involving the host response.

– Recommendations

The scientific committee recognizes that this G5 junior group has developed a unique expertise based on original and novel data. The team leader has a rising international visibility, has obtained an ERC starting grant and this funding should be used to recruit additional lab members.

The interface between basic molecular Science, in vivo infection and drug development gives a good image of the Institut Pasteur tradition.

The group should be careful not to give too diverse orientations in its research activity and not to dilute its visibility. The project on immune response could be more focussed on PG and the group may be encouraged to develop models more representative of Leptospira infection.

In conclusion, the scientific committee will be fully in favour of the transformation of the G5 group into a full unit.

Title of the team : Molecular Genetics

Name of the team or project leader: M. Anthony PUGSLEY

- Staff members

	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	6
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5
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 2.8 of the application file)	
N7: Number of staff members with a HDR or a similar grade	5

This unit was created 8 years ago (12 years term in December 2013) around two themes, and two group leaders. That is the head of the unit (60 years old, Professor IP, h-index 49, more than 200 publications) working on pullulanase secretion (now on secretins), and another permanent scientist (54 years old, DR2 CNRS, h-index 18, 27 publications) working on the MalT regulon together with another scientist (CR IP, 42 years old, h-index 9, 12 publications). The unit evolved by giving other younger permanent scientists (CR IP, 41 years old, HDR in 2007, h-index 9, 16 publications; and CR IP, 47 years old, h-index 13, 24 publications, HDR in 2008,) their own research line (Lipoproteins and Type II Pseudopilus, respectively). Another permanent scientist joined the unit in 2007 (50 years old, CR IP, h-index 20, 32 publications, HDR in 2003) studying Crl chaperone and RpoS sigma factor. In total, current members of the unit thus include six researchers (1 Professor, 1 DR2 and 4 Assistant Professors), two technicians, 1 engineer, 1 secretary and 1 kitchen assistant. Each group within the unit presents a good balance of Staff, PhD, post doc and technician.

- Appreciation on the results

This is an outstanding unit directed by a charismatic leader who is a pioneer in the field of protein secretion. The unit is composed of five small groups, each of them with good to very good scientific production. The themes of the groups are 1) stress responses mediated by the sigma S transcription factor, 2) structure and function of the STAND signal transduction proteins, 3) biochemistry of lipoprotein synthesis, 4) type 2 secretion systems and assembly of pseudopilins, and 5) type 2 secretion systems and structure and function of secretins.

For the reporting period (2006-2010), the unit has been highly productive with 40 articles and reviews published in international journals with an editorial board. The Assistant Professors have demonstrated relative independence from the head of the unit as evidenced by authorship on publications (25 of the publications were not signed by head of unit). Highlights include articles published in *Biochemistry*, *EMBO J* (x2), *J Mol Biol*, *Mol Cell* and *PNAS* (x2). Much of the remainder of the work was published in top specialty journals in the field (17 articles in J *Bact* and *Mol Microbiol*).

The unit has developed an extensive network of collaborators that is bringing complementary expertise including structural biology and cryo-electron microscopy.

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

The head of the unit has demonstrated an outstanding contribution to the dissemination of knowledge both by being invited to major international conferences (48 since 2006 including Gordon Conference, ASM etc…), but by being himself a major organizer of key conferences in his field (EMBO Summer school on membranes in Cargese, EMBO conference on Protein traffic in Sainte Maxime-2008). He has also be the senior editor for Molecular Microbiology and the chairman of EMBO Long-term fellowships committee. The other members in the group could be more active in particular by being invited to major international conferences, which is not always the case.

The unit has attracted significant funds in the past including European funding. During the period (2006-2010) funding from Pasteur Institute, FRM and in particular 4 ANR grants are to be highlighted. Three of these ANR are still active including two until 2013. These funds have been attracted quite equally by the different subgroups. A long term EMBO fellowship has also be obtained by the group working on pseudopilus.

- Appreciation on the scientific strategy and the project

The projects for the next four years are built on ongoing research. Important goals include elucidating the mechanism by which sigma S negatively regulates gene expression, molecular analysis of inhibitors/inducers of the STAND proteins, development of screens for inhibitors of lipoprotein synthesis, generation of structural models for pseudopilins and their validation by mutagenesis, and analysis of secretin structure by cryoelectron microscopy and X-ray crystallography.

- Conclusion:

  – Summary

The head of the unit is a world class and recognized scientist, who has achieved exceptionally in his field (protein transport across the bacterial cell envelope) being among the highly cited researchers. He has provided excellent training to his people and also to the overall community by organizing majors and regular conferences. The activity of the unit is broad but well split between individual group leaders. Other group leaders in the unit do not have international profile track record, but they are younger and will have the possibility to further develop.

  – Strengths and opportunities

The team leader is a charismatic scientist, he has been a pionneer in his field and largely contributed to the dissemination of Science in his research area.

The team leader has done a very good job at organizing his team into 5 groups which have been highly productive and have demonstrated relative independence.

  – Weaknesses and threats

The future of the unit, as it is now, at the end of the 12 years mandate (December 2013) remains uncertain due to the lack of an obvious successor to the current leader.

  – Recommendations

The research activity of the unit is of excellent quality and the scientific committee does not foresee any slowing down of this activity in the next three years, which will correspond with the end of the 12-year mandate (December 2013). Although the Assistant Professors are very good scientists and despite the high quality of the work done within each group, none of them has yet emerged as an obvious future leader of a unit. The committee believes that they should be encouraged to do so, and that they need to take a proactive role in what is likely to be a major restructuring at the end of the unit mandate (December 2013).

Title of the team : Biology of Gram-positive Pathogens

Name of the team or project leader: M. Patrick TRIEU-CUOT

- Staff members

	Future
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)	6
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4
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 2.8 of the application file)	
N7: Number of staff members with a HDR or a similar grade	5

The unit was created in January 2004 and was originally composed of two teams working on the important human Gram-positive bacterial pathogens. The team leader (56 years-old, CL-IP, h-index 39, 112 publications) headed the *Streptococcus* group, whereas another permanent scientist (48 years-old, CL-IP, h-index 26, 50 publications) headed the *Staphylococcus* group. In 2008, a formal unit of the CNRS URA2172 (E8) headed by a permanent scientist (62-years-old, CL-IP, h-index 23, >40 publications) working on *Streptomyces* was administratively associated with the unit. The scientist heading the Streptomyces group will retire in 2013 and will not thus be able to take full part in the next unit mandate (due to last from 2012 to 2015). In 2009, another team headed by a permanent scientist (57 years-old, CL-IP, h-index 27, 75 publications) and establishing research on nosocomial enterococcal infections was also associated with the unit. In 2010, the unit included 17 members including 7 senior scientists, 2 PhD students, 3 postdoctoral fellows, 1 engineer, 3 technicians, and 1 secretary. Of note, a senior scientist (PU-PH) who is a team leader at the Cochin Institute is also working 10% of her time in this team. For the next 4 years, the unit will be organized in 3 groups working on *Streptococcus*, *Staphylococcus*, and nocosomial infections, respectively. The team leader has an international reputation and is inspiring for younger scientists in his unit. Besides the already established leadership of the scientist heading the *Staphylococcus* group, the head of unit is giving the possibility to younger brilliant scientists in the *Streptococcus* group to emerge. That is the case of a permanent scientist (42 years-old; Chargé IP, h-index 22, 36 publications) who recently published, as last author, a seminal work on the dual role of *Streptococcus agalactiae pili* (PLoS Pathogens, 2009, IF 9,2).

- Appreciation on the results

The main research goals are to elucidate new pathways/mechanisms involved in the pathogenesis of *Streptococcus* and *Staphylococcus*. The research topics include studies of bacterial surface components involved in interactions with the host, of relationships between metabolic adaptation and virulence, and gene regulation in relation to host environment and adaptation to stress responses. A few highlights of the research conducted in the group include (a) seminal work on biosynthesis and assembly of *S. agalactiae* pilus, as well as establishing its role in adherence and biofilm formation (see above), (b) identification of a novel streptococcal adhesin contributing to the enhanced neonatal colonization potential of the hypervirulent *S. agalactiae* ST17 clone (this is a brilliant example of the outcome coming from the collaboration between the team leader and the Cochin clinician; J. Exp. Med, 2010, IF 15,3), and (c) new insight into the two-component system WalK/WalR in the control of cell wall metabolism and biofilm formation in *S. aureus* . In conclusion the research has considerably advanced our understanding of the pathogenesis of these important pathogens and the results are highly clinically relevant through identification of novel therapeutic candidates as well as insight into efficacy of antimicrobials. The work on nosocomial enterococcal

infections aims to study population structures of E. facaelis strains in order to identify genes that are important during infection and colonization or exposure to antibiotics. The project is based on collections obtained through the national reference center and through collaboration with clinicians.

The team has published a total of 43 peer-reviewed papers, out of which 33 were published in journals of Q1-level, during 2006-2010. First and/or last author papers included publications in PLoS pathogens (2009a, 2009b), Journal of Bacteriology (2009, 2007), Emerging Infectious Diseases (2008), J Immunol (2008), Journal of Clinical Microbiology (2007), Infection and Immunity (2007), Molecular Microbiology (2009, 2008a, 2008b, 2006), Advances in Experimental Medicine and Biology (2008), Microbiology (2008, 2006), Arch. Microbiol (2006). Several outstanding papers have been published with the last author being the senior scientist who is both a team leader at the Cochin Institute and a part-time member of this team. These papers include a letter to Nature (2009) and a paper recently published in The Journal of Experimental Medicine (2010).

The work of the unit has also resulted in two international PCT patents and several PhD theses.

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

Most members of the team have important roles in the research evaluation process both nationally and internationally, which shows recognition and leadership in their field. Briefly, this includes: CNRS evaluations committees, INRA evaluations committees, Institut Pasteur internal scientific review board (COMESP); international: external referee for research projects from the National Agency of Portugal, members of editorial boards (Mol. Micro, J Bact, AAC. Commissions of trust: scientific head of the "DIM maladies infectieuses et nosocomiales emergentes", member of the Scientific council of the Pasteur Institute; vice-president of COMESP; Associate editor of Microbiology and BMC Microbiology. One young member of the staphylococcal group (38 years-old, Chargé IP, h-index 9, 15 publications) received the Jacques Monod Prize in 2004.

The team leaders for the streptococcal and staphylococcal team are internationally recognized experts within the field, with demonstrated ability to raise funds both nationally and internationally including an impressive number of EC-funded projects. The funds they raised since 2004 are beyond 2,5 M € in total. This includes two ANR grants starting in 2011 for over a period of 3 years.

The team participates in large European networks, as well as with researchers/clinicians both nationally and internationally. These collaborations are well chosen and should contribute with excellent model systems and/or complementary knowledge.

- Appreciation on the scientific strategy and the project

The future perspectives described in the research plan are novel, hypothesis-driven and of high clinical relevance. Feasibility is promoted by the team's track-record and the fact that several of the new perspectives build on the groups own recent findings, as well as their established collaborations with excellent researchers and clinicians ensuring access to state-of-the art techniques/model systems as well as access to clinical samples.

- Conclusion :

  – Summary

The team has an excellent track record within the field of Gram-positive bacterial pathogenesis and the team included several young and promising researchers. This is important to highlight since it guarantees a real dynamic in the unit and the possibility of blossoming new units in the future. The addition of the two associated teams though has not added any significant scientific values to the actvity of this unit.

  – Strengths and opportunities

The unit has several permanent scientists with great potential.

The unit is working on major human pathogens and are addressing clincially relevant issues.

The unit provides an excellent example of research covering both fundamental and clinical research.

– Weaknesses and threats

The added value of the two associated groups working on Streptomyces and nosocomial infections is not obvious.

As other groups at the Pasteur Institute, some of the members of this unit need to have access to carbohydrate fine structural analysis platform.

– Recommendations

The scientific activity of the unit is international level. The interface between basic Science and clinical research is very productive and should be further encouraged and supported.

The work presented by the team leader for the Streptomyces group raised a lot of interest in the committee as it may have potential for future directions in novel antibiotic development. Although, this focus does not fit in this unit, antibiotic resistance and novel agents is definitely a field in which the Pasteur Institute should partake in by implementing new modern concepts. How this activity should be reorganized and not lost should be considered carefully.

In conclusion, the scientific committee feels that the high scientific productivity and quality of the research conducted at this unit definitely warrants continued support of the unit.

Title of the team : Toxins and Bacterial Pathogenesis

Name of the team or project leader: M. Pierre GOOSENS

- Staff members

	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1
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 (Forms 2.2, 2.4 and 2.7 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 engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0
N6: Number of Ph.D. students (Form 2.8 of the application file)	2
N7: Number of staff members with a HDR or a similar grade	2

The former team leader of this unit (Michele Mock) has recently retired and the unit will be closed. The new independent laboratory is a spin out of this unit. It is now led by one of the permanent scientist (56 years-old; Chargé IP; 33 publications) of the previous unit who acts as a PI. The new laboratory includes presently one other permanent scientist (54 years-old, DR2 CNRS, 57 publications) and a "Maitre de Conference (Paris XI) who were also a member of Michele Mock's unit. The laboratory includes also a national reference center for anthrax whose deputy director is an engineer (IP) also in charge of the BSL3 facilities. Since 2007, another permanent scientist was temporarily associated with Michele Mock's unit for administrative reasons, but will postulate for the creation of an independent unit to be associated with the CNRS URA2172, and will not be discussed in this section. The laboratory is also hosting another engineer (IP) and 2 PhD students.

- Appreciation on the results

The former team leader (M. Mock) belonged to the leading experts in the field of Bacillus anthracis, the causative agent of anthrax. Under her guidance the team has performed highly recognized work on the spore surface structure, the biodiversity of this important pathogen, the recently identified *B. anthracis*-like *B. cereus* strains, the regulation of the major virulence genes (coding for capsule and toxins) and the innate and adaptive immune responses triggered by *B. anthracis* in murine models.

The two latter aspects are now continued and extended by two former permanent scientists from the M. Mock's unit, one of which is the new group leader. Of major importance are the new research activities aiming to analyse (a) the connection of the metabolism and global metabolic regulators (e.g. CodY) with the expression of the toxin and capsule genes via the virulence regulator AtxA (this project is performed by the permanent scientist who is not the laboratory head), and (b) the subversion of innate immune response by the *B. anthracis* toxins and the involvement of the humoral (toxin-neutralizing antibodies) and cellular immune responses (anti-spore IFN-gamma secreting CD4 T lymphocytes) in the adaptive immunity against this pathogen (performed by the new head of the laboratory). The latter finding is novel and may be of major relevance for the development of future vaccines against anthrax.

The team has published several first/last author papers in respected (Q1) journals including articles (most of them still together with M. Mock) in Res Microbiol (2010), Appl Environ Microbiol (2009), Inf. Infect (2009), J. Infect. Dis (2009), Can J Microbiol (2009), Microbes Infect (2008, 2007), Plos Pathogen (2007), J. Immunol. (2007), Microbiology (2007a, 2007b), Cell Microbiol (2007).

Unit members have also been invited to write reviews in Journals such as Curr Opin Microbiol (2006), Mol Microbiol (2006), Mol Aspects Med (2009)and Res Microbiol (2010).

Taken together the reseach activities of both permanent scientists are of high quality.

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

The former leader enjoyed a high international reputation as a leading expert in the anthrax field with many international connections and collaborations. The new leader has not yet reached this outstanding international level, but seems to have the potential to develop into a successful unit leader with a strong own scientific profile. In the last two years he published several papers in which he has main and independent authorship such as J. Infect Dis (2010; IF 5,7); PLoS pathogen (2009; IF 9,2). The other senior scientist of the new laboratory also published independently as senior author such as in Res. Microbiol. (2010, IF 2), Infect Immun (2009, IF 3,9). She is also Editor in chief for Microbiology. Both are presenting their work at international conferences on Immunology of Anthrax, Spores, Bacillus-ACT or European congress of Immunology. Both will likely need to secure further funding for the laboratory.

- Appreciation on the scientific strategy and the project

There are several novel and interesting futural perspectives in the projects proposed by the two team leaders for the next 4 years: (a) mechanism of CodY on AtxA activity and hence on virulence gene espression of *B. anthracis,* especially under the influence of in vivo infection parameters, (b) the dynamics of the host-pathogen interactions and the immune control of *B. anthracis* infection in suitable *in vivo* models. These proposals are original, experimentally feasible and of high scientific (and potentially medical) relevance for the anthrax field.

- Conclusion:

  – Summary

This unit has been formerly headed by a charismatic scientist who was a leader in the anthrax field. The *B. anthracis* research is now in the hands of two permanent scientists, who are 56 and 54 years old and possess (based on their publication records and international visibility) a high, but not yet outstanding international scientific standing. The sustainabilty of this unit under the leadership of P. Goossens therefore remains still to be established.

  – Strengths and opportunities

- The new team leader has published several good last author publications during the past 4 years.

- The two permanent scientists have excellent complementary expertise in the field of *B. anthracis*

- The novel findings on the interactions between metabolism and virulence gene expression in *B. anthracis*, and the deeper understanding of the immune responses against this important pathogen are original and interesting

  – Weaknesses and threats

- Given the early state of this new independent laboratory, sustainabilty and leadership potential of the new team leader has yet to be proven.

  – Recommendations

- The laboratory needs to demonstrate that it can maintain its international visibility. It needs to show a potential for innovation and originality in a research field dominated by M. Mock in the past years.

- The group leader may want to consider broadening subjects, for instance by studying related pathogens such as *Bacillus cereus*

- Clinical relevance could be increased by incorportating human cell and tissue models to validate mouse date.

- In conclusion, the scientific committee feels it is too early to evaluate the independent activity of a laboratory recently restructured, but is confident the team leader may do a very good job.

Title of the team : Biology of Spirochetes

Name of the team or project leader: M. Mathieu PICARDEAU

- Staff members

	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	
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 (Forms 2.2, 2.4 and 2.7 of the application file)	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2
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 2.8 of the application file)	
N7: Number of staff members with a HDR or a similar grade	1

The team was created in January 2007 as a provisional unit and is thus due for evaluation at the end of 2010. If the unit is confirmed, it will then postulate to be one unit of the CNRS superstructure (URA2172), which will include a total of 10 units. The provisional unit currently includes a national reference centre (NRC) for Leptospirosis and a research group. The ETM is 10, with 5 persons associated with the national reference centre and 5 working in the research group. The team leader (40 years-old, IP, h-index 19, 58 publications) is head of both the unit and the NRC. Other permanent positions of the research group include two part-time positions (40% engineer and 50% technician), and a scientist who joined the team in January 2010 (43 years-old, Chargé IP, h-index 10, 17 publications). Two post-docs have been working for shorter time periods (12 and 18 months) in the group.

- Appreciation on the results

The team has focused on advancing the field of genetics of *Leptospira*, thereby providing for the first time genetic evidence for a virulence factor of this pathogen. The team has also been involved in the sequencing of the complete genome of the saphrophyte *Leptospira biflexa*. Comparison of this genome to that of pathogenic *Leptospira* species have provided clues as to the lifestyle of *Leptospira* in the environment and in the infected host.

The main function of the NRC for leptospirosis, which is also a WHO collaborating centre, is surveillance in mainland France as well as in French overseas territories. Two recent outbreaks have been evaluated by the team revealing ten novel potentially pathogenic *Leptospira* genotypes.

The team has published a total of 25 papers during 2006-2010, including several first/last author papers in Journals such as PLoS Negl Trop Dis (2010), Appl Environ Microbiol (2010), Microbes Infect (2009), Infect Immun (2009, 2008, 2007), J Med Microbiol (2009), Microbiology (2008), PlosOne (2008), BMC Microbiol (2008), Infect Immun (2008), Plos Pathog (2007), J Clin Microbiol (2006), J Bacteriol (2006a, 2006b).

In addition, the team leader has been invited to write reviews in journals such as Nat Rev Microbiol (2009), Infect Genet Evol (2009), Appl Environ Microbiol (2008), Curr Protoc Microbiol (2007) and Genetica (2010).

Invited external reviews provided by experts in the Spirochete field were all highly positive to the research conducted by the team leader.

- 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 been repeatedly invited as a speaker at Gordon research Conferences on biology of Spirochetes, as well as several national and international conferences/seminars.

The team leader has participated in lab evaluations at the University College of Dublin for Science Foundation Ireland, and is Associate editor of PLoS Neglected Tropical Diseases.

The team leader has obtained several grants including from the ANR (MIE, Young Scientists), the Institut National de Veille Sanitaire, The Ile-de-France Regional Council, and the Flocruz Foundation.

The team is one out of 10 teams taking part in a large-scale genome sequencing of Leptospiral strains funded by NIAID and the Genome Sequencing Centres for Infectious Diseases program.

- Appreciation on the scientific strategy and the project

The team has developed some valuable tools (transposon-mutagenesis, shuttle vector, animal model) which will help to unravel the biology and virulence properties of this emerging, but still poorly understood group of pathogens. The future perspectives presented in the report were still rather vague and not sufficiently hypothesis-driven. This makes the feasibility of the proposed projects somewhat difficult to assess. However, the fact the team has the above-mentioned tools, as well as other appropriate experimental expertise (e.g. imaging technologies, access to large scale Leptospira genome sequencing data) should promote substantial progress in the molecular analysis of the virulence mechanisms.

- Conclusion :

  – Summary

This team is focusing on Leptospirosis, wich has been emphasized as an increasingly public health problem. The focus is on unraveling the biology and virulence of pathogenic *Leptospira*. The team leader is a recognized leader in the leptospiral field, who has conducted pioneering work on developing tecnhniques to genetically manipulate this pathogen. This is a major advance in the field as it provides the essential tools for future studies and advances in the field.

  – Strengths and opportunities

- The team leader is young and has a very good track record.

- This team has made a strong investment in successfully developping genetical tools to identify *Leptospira* virulence factors.

- *Leptospira* represents relevant emerging pathogens and is historically associated with Institut Pasteur research.

  – Weaknesses and threats

- Given the rather small size of this provisional unit, the research proposal involves too many different aspects without clear focus and well-defined working hypotheses.

  – Recommendations

- The committee recognizes that this team has done pioneering work on the development of genetic tools for work with *Leptospira*. This is a major advance in the field and opens up new possibilities to unravel virulence mechanisms of this pathogen.

- The team leader now needs to demonstrate his ability to utilise these tools in an innovative approach to decipher viurlence mechanisms of *Leptospira*.

- Care has to be taken to avoid diversification into too many areas, but rather to focus on virulence aspects of pathogeneic Leptospira and advance in an hypothesis-driven manner.

- In conclusion, the committee will support the transformation of this provisional unit into a full unit but the development of aspects mentionned above should be carefully reviewed in 4 years.

Title of the team : Anaerobe pathogenesis

Name of the team or project leader: M. Bruno DUPUY

- Staff members

	Future
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)	3
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2
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 2.8 of the application file)	
N7: Number of staff members with a HDR or a similar grade	2

This is a new team (created October 1st, 2010) that includes a team leader (50 year-old, chargé IP, h-index 15, 27 publications) who has worked on Clostridium, who will be joined by two other permanent scientists (49 year-old, PR1-Paris 7, h-index 22, 45 publications and 36 year old, MCU-paris 7, h-index 12, 23 publications) with teaching duties who have previously worked on *Bacillus subtilis* and *Staphylococcus aureus*. These two scientists were previously associated with the unit directed by Antoine Danchin. The team has been created for two years following on the retirement of Michele Mock to whom the team leader was previously associated. Be this new team further confirmed, the team leader would like to join the new CNRS URA2172.

- Appreciation on the results

The laboratory focuses mainly on *Clostridium difficile* (Cd) a major public health problem because of its role in the nosocomial infection pseudomembraneous colitis. Hospital outbreaks in USA and UK have emerged over the past decade and have been associated with hypervirulent clones.

The team leader main research is on the genetics of *Cd toxin* regulation. In particular, he has studied the tcd pathogenicity locus, a set of 5 genes located on a 20Kb element acquired by horizontal transfer. BD's major contribution has been to identify that *tdcC* is an anti-sigma factor, absent in hypervirulent clones of *Cd* and one important (but not the only) factor implicated in increased toxin production.

The team leader work is very well complemented by the impressive research of the other two permanent scientists, and especially the PR1-Paris7 deserves much praise for her excellent contributions and supporting role in the lab. Her background is in the biology of Gram positive bacteria and in global regulation mechanisms linked for example to catabolite repression and cysteine inhibition. Her rapid adaptation to the field of Cd is impressive.

The team members have published several first/last author papers during the past 4 years including in Plos Pathogen (2010), FEMS Microbiol Lett (2010), BMC Microbiol (2010), Methods Mol Biol (2010), Mol. Microbiology (2009, 2007), J Med Microbiol (2008), J Biol Chem (2008), NAR (2008), J. Bact (2007, 2006). Some of these papers focused on *Clostridium* while others were related to work on *Bacillus subtilis* or *Staphylococcus aureus*. The main highlights are the contribution of the team leader to the release of the *Cd* mosaic genome (Nature Genetics, 2006) and the mre recent paper by the other two permanent scientists (first and last author) published in PLoS pathogens (IF 9,4) 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 leader has been invited to some national and international conference on Clostridium so was the other permanent scientist on Bacillus.

The team has obtained grants from the ANR (2 as a co-investigator), the NIH (as a co-investigator), from the ERA-NET and from the Pasteur Institute (2 PTR grants).

- Appreciation on the scientific strategy and the project

The immediate future of this laboratory is very promising. The research is impressive and the oral presentation to the Site Visiting Committee was dynamic, exciting and original. The chemistry between the two main scientists in the team is excellent and their evident synergy has impacted very positively on the rest of the group who are very well engaged and cohesive. Te head of the laboratory has demonstrated very good leadership skills and the whole research group has an impressive momentum.

- Conclusion :

  – Summary

This is a recently formed group with a team leader restructuring his activity afetr being in previous units in which the PI moved or retired. The team leader focus on the Clostridium genetics. Under the circumstances of this restructuration the team leader was associated with another permanent scientist, who brought in the group her expertise on regulation/physiology in Gram positive bacteria. The chemistry between the two scientists appears to be appropriate and the perspectives of this project are excellent. Time should be given to the head of the group to demonstrate his leadership and to improve his track record to higher international profile. If the unit was to be confirmed the wish is to join the new CNRS URA2172.

  – Strengths and opportunities

- Originality and quality of the science that was performed within the recent period

- The team leader demonstrates leadership potential

- The chemistry between the team leader and the other permanent scientist within the group appears to be excellent

- The associated permanent scientist has independently made superb contributions during this short period. Furthermore, the group is working very well together

- The choice of *Clostridium difficile* as a pathogen of public health importance is relevant.

  – Weaknesses and threats

- The team leader needs urgently to increase his personal publication record.

  – Recommendations

In conclusion, the scientific committee recommends continuation of the Group (no expansion of personnel) and if research productivity is maintained and reflected in appropriate future publications, then the case for a Unit would be strong. The only caveat is that the team leader does not yet have a strong publication record (~27 peer reviewed original articles) and is arguably not yet established as having a secure international profile. Thus, he needs to capitalise rapidly on the current good research he is leading. It was noted that the associated permanent scientist has a better track record and should the team leader performance not prove satisfactory, she has excellent potential. However, the committee felt that the current head of the group should be supported strongly in view of the excellent progress and performance of the current research group as it is currently structured.

Title of the team : Yersinia

Name of the team or project leader: Ms. Elisabeth CARNIEL

- Staff members

	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	
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 (Forms 2.2, 2.4 and 2.7 of the application file)	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5
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 2.8 of the application file)	
N7: Number of staff members with a HDR or a similar grade	1

This unit includes a National Reference Centre, a WHO Collaborating Centre for *Yersinia*, and a National Surveillance Network for enteropathogenic *Yersinia*. This is reasonably sized team including the head of unit (h-index 31) and two assistant professors (h-index 13 for about 40 publications and h-index 18 for about 30 publications). In addition there are currently two PhD students, one master student, one veterinarian fellow and one postdoctoral fellow in the group. There are two engineers and two technicians as well as one secretary.

- Appreciation on the results

The team leader has organized her group into a focused team that does state of the art fundamental research on *Yersinia* as well as public health work. She uses the reference centre productively. She has done well to interconnect research on mechanisms of pathogenesis with evolution and epidemiology. She accomplishes much with a relatively small team by extensive collaborations. The team appears to be cohesive and energetic, producing significant studies on all three pathogenic *Yersinia* species.

The three major activities of the team are well defined and highly relevant. First, they will continue their groundbreaking work on *Yersinia* evolution and microevolution. The finding that Y. *pestis* is a recently emerging clone of Y. *pseudotuberculosis* was ground breaking and opens many opportunities for comparative analyses to define the genetic bases for the widely different epidemiological and pathogenesis characteristics. Y. *pestis* evolution involved a large burst of internal recombination and insertion element activity and its genome is quite unstable. In addition, extensive genome sequencing is being done to enable reconstruction of the phylogenetic history of *Yersinia*. They proved that at least two strains of Y. *pestis* were indeed the cause of the Black Death and could trace the spread of plaque along the Silk Road and the sea navigation routes from a possible origin in China. They also have unravelled the breaching evolution of Y. *pseudotuberculosis*, which is far more polymorphic than Y. *pestis*. Second, the study of mobile genetic elements brings her team directly into the exciting area of horizontal gene transfer and evolution of pathogens. This effort fits well with the first activity on evolution of these organisms. Much novel work is proposed. For example, the group will do more studies building on their surprising finding of a virulence locus in all branches of Y. *pestis* encoding a filamentous phage. The mechanism of virulence stimulation, the molecular biology of phage replication, and the stabilization of the integrated prophage are under study. The extreme virulence of Y. *pestis* is remarkable. The group has identified several widespread mobile elements associated with virulence and drug resistance and is studying how mobility is controlled. The group proposes innovative experiments on comparative pathophysiology of Y. *pestis* and Y. *pseudotuberculosis* using rodent models (a natural host). Bioluminescent strains have been established and will provide powerful tools to study pathogenesis. The final activity focuses on the fact that Plaque is re-emerging. Therefore the proposed basic public health studies to improve the control of plague and other yersinoses through modern surveillance, diagnostics, and infection controls are highly relevant. The studies

directed to develop an oral live attenuated Y. *pseudotuberculosis* vaccine against both forms of Plague are exciting and pose several new avenues for study. The experiments designed to identify genetic susceptibility loci in mice to *Yersinia* have found at least three large loci that will be further dissected. These studies are done with the mammalian genetics group at the Institute and are likely to uncover new mechanisms of resistance to *Yersinia*. The national and international surveillance work and outbreak investigation plans are well developed. Given the status of re-emerging *Yersinia* infections in the world as a major human and animal disease problems, this work is highly relevant.

Since 2006 the members of the team have contributed to at least 38 peer-reviewed publications many in top journals, though much of the work is with collaborators. The work published in 2010 in Nature Genetics (Plague out of China) is one highlight of this remarkable production. Other publications are regularly appearing in PLoS genetics, Mol. Micro, AAC, PLoS Medicine, Infect Immun or J. Clin Microbiol.

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

The *Yersinia* unit has attracted a significant of funds over the last years essentially though NRBC programme (terrorism) but also by collaboration with pharmaceutical companies (Aventis, Bertin) or from the Institute of Sanitary surveillance.

The team leader is invited at international meeting such as the ASM general meeting (2009) at which she also gave a press conference.

There are well established collaboration with other leader in the field including J. Hinnebush (Rocky Mountains), M. Skurnik (University Turku) or J. Hacker (Robert Koch Institute).

- Appreciation on the scientific strategy and the project

The unit working on *Yersinia* pathogenesis is innovative, and of the highest quality. This unit has a unique combination of expertise to understand the biology, pathophysiology, and evolution of these remarkable pathogens. The people within the group are engaged and interactive. In particular, they have demonstrated their ability to identify and understand those genetic changes that yield the extreme pathogenicity of Y. *pestis*. They also have demonstrated capability to leverage international collaborations in sequencing and to engage productive international public health efforts in epidemiology. The WHO collaborating centre/reference laboratory efforts are well integrated and valuable not only for their research, but also for the international community. Given the team leader's record and her diligence in directing a highly interactive and productive team, the impact certainly will continue.

- Conclusion :
  - Summary

This unit is near the end of its second four-year mandate. It is an excellent group that has shown a cohesive and energetic activity, combined with an excellent production. This is highlighted by a very good publications track record during the past 4 years some of them in top journals. The proposed research is focused and likely to yield important fundamental results.

  - Strengths and opportunities

Cohesive and energetic team.

Stimulating group leader.

Very good publications during the past 4 years including some in top journals.

Unique combination of expertise.

The team has demonstrated an exceptionnal capability to engage in productive collaborations.

– Weaknesses and threats

None

– Recommendations

The scientific committee recommends continued support for another four years with considerable enthusiasm.

Title of the team : Genetics of Biofilms

Name of the team or project leader: M. Jean-Marc GHIGO

- Staff members

	Future
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)	2
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2
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 2.8 of the application file)	
N7: Number of staff members with a HDR or a similar grade	2

This unit was created in 2007, and is thus approaching the end of the first 4 years mandate. It is a follow up from a previous G5 group. The group is headed by an established scientist (46 years old, Associate Prof IP, h-index 25, 52 publications) who has developed a completely novel area of research at Pasteur (Biofilm). The unit benefits from the activity of another permanent staff (39 years old, CR IP, HDR in 2008, h-index 14, 26 publications), who joined the group in 2001 when it was still a G5. This scientist is supervising a significant proportion of the people in the unit. Overall it is a large group with 2 engineers with significant scientific track record. One engineer (previously in C. Wandersman unit, 48 years old, IP, h-index 21, 35 publications) joined the unit in 2009 whereas another IP engineer (43 years old, h-index 5, 6 publications) already joined the G5 group. In addition 4 Post docs and 3 PhD were listed as members of the unit at the time of the evaluation.

- Appreciation on the results

The group leader has developed a completely new area of research at Pasteur and became one of the world expert in the molecular aspects of biofilm formation using *Escherichia coli* as a model but also other bacteria including pathogens, commensal and probiotics. His track record is outstanding and he is invited in the most relevant international conference on Biofilm. He will also Chair the Gordon research conference on microbial adhesion in 2013.

The research activity spreads essentially on 4 general research themes, which are: (i) New factors promoting biofilm formation, (ii) Gene expression and biofilm lifestyle, (iii) competitive bacterial interaction in mixed biofilms, (iv) Biophysical aspects of surface contacts.

The team has published several first/last author papers during the past 4 years including in Mol. Microbiology (2009), J. Bact (2008a, 2008b, 2006), Plos Biology (2008), Environmental microbiology (2010), Applied and environmental microbiology (2007), PNAS (2006). The team members have also been co-authors in journal such as PLoS Genet (2009) and have been invited to write a review in Current Topics in Microbiology and Immunology.

- 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 an obvious international visibility and is invited at several international conferences (22 international and 14 national since 2006). He has been nominated chair for the Gordon research conference on Microbial adhesion and cell signalling in 2013, which is quite prestigious.

Four patents are held by the group revealing the strong commitment with industry.

Funding is also a strength of the group. Current grants are also from industrial partners such as Saint Gobain (surface adhesion), or involves clinicians such as with DIM Maladie (infection noscomiale), Pasteur/Curie (Infection nosocomiale). There is also significant EU funding in the past showing extensive international collaborative network. One other indication of the international visibility of the team is that four postdocs from different nationality have worked in the lab for the past four years.

- Appreciation on the scientific strategy and the project

The research activity of the group shows not less than 7 specific research themes including: (i) Gene regulation during biofilm formation, (ii) Plasmids and Biofilm formation (the leader published a seminal paper in Nature on this topic in 2001), (iii) The extracellular matrix, (iv) The arsenal of adhesion factors, (v) Mixed biofilms, (vi) Community associated metabolites, (vii) New approach for early interaction of bacteria with surfaces. It is remarkable that for most of these projects novel findings have been obtained based on original strategy and cutting edge methodologies. This cleverness in the design of the experimental approach is a trademark for this unit.

The future projects are mostly based on the continuation of these activities. Project 1 is a collaboration with Institut Curie and study the response triggered by bacterial contact on a surface using glass slide (Affymetrix). Project 2 is looking at lectomes or at the comprehensive identification of the set of lectins (mostly associated with fimbriae) involved in attachment. The project also addresses their specificity versus carbohydrates. Project 3 is addressing the role of c-di-GMP in the production of the extracellular matrix in biofilm. Project 4 uses RIVET to identify genes specifically expressed in biofilm when subjected or not to antibiotic treatment. This is important knowing that antibiotic tolerance is one hallmark of biofilms. Project 5 uses more than hundred E. coli strains (commensal or pathogenic) and searches for molecules, produced by these strains, that will interfere with biofilm formation of other bacteria. The group has been previously successful with this kind of approach (PNAS, 2006). Project 6 is to monitor invasion of fluorescent bacteria using an in vivo model of biofilm infection in rat (collaboration Hopital Marie-Lannelongue) with implanted port vascular catheter, which increases the interaction with clinician.

- Conclusion :
  - Summary

This unit is a follow up on a very successful G5 group. This group is headed by a brilliant and intrenationally visible scientist who has establisghed a new area of research at Institut Pasteur (Bacterial biofilm). The leader has done an excellent job in structuring his team and in supporting the independent development of a younger scientist in his unit. The research activity has resulted in high quality publications and establishment of a solid network of collaboration with industry and clinicians. The experimental approaches are cutting edge and the team leader demonstrates his ability to take new methodologies on board as they appear.

  - Strengths and opportunities

The team members have given high quality presentations.

This is a good size and well equilibrated team.

The permanent researcher working in the team was given the opportunity to develop his own projects.

The team develops ingenious, innovative and clever experimental approaches.

The team leader is relatively young and has succesfully developed a completely novel research area at Pasteur Institute.

The team leader has quickly acquired international visibility in his novel research field.

The team has developped a strong multidisciplinary approach and has established strong connections with industrial partners and clinicians.

– Weaknesses and threats

The team is tackling many different issues and there is a significant risk of dispersion.

– Recommendations

The scientific committee was impressed by the high quality of this research unit, which obviously is on a very positive momentum. Although the research projects are already too numerous, and that clear priorities should be given in future prospects, the committee feels that further emphasis on the host could be favoured. Seeking for expertise in this particular area may justify the recruitment of a new staff member. The fact that the unit will move from Fernbach to renovated Fourneau building is also very positive. In conclusion, the research activity of the group is very productive and ingenious, maybe too spread, but innovation is a strength and should be encouraged. The scientific committe recommends without the slightest hsitation the further continuation of the unit for another 4 years mandate.

Title of the team : Cyanobacteria collection

Name of the team or project leader: Ms Muriel GUGGER

- Staff members

	Future
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 (Forms 2.2, 2.4 and 2.7 of the application file)	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0
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 2.8 of the application file)	
N7: Number of staff members with a HDR or a similar grade	0

- Appreciation on the results

The collection of approximately 750 cyanobacterial strains was established by Dr. R.P. Stanier within the Pasteur institute. Cyanobacteria, oxygenic photosynthetic prokaryotes, largely contribute to the balance between CO2 and O2 in the atmosphere. Adapted to a wide range of environmental conditions, they colonize most ecosystems. Their occurrence as water-blooms disrupts the equilibrium in continental aquatic ecosystems, but also may be harmful to animals and man. The collection, which is part of the Pasteur Institute Biological Ressource Center (CRBIP), is a valuable source and has been the focus for studies of diversity, phylogeny, ecology and physiology of cyanobacteria and included the development of molecular tools for risk assessment associated with the presence of toxic strains in water resources. The research was performed by staff members, by master of science and Ph.D. students from French universities, and in collaboration with external partners in France and internationally. The work has included diversity studies based on 16S rRNA sequences and lately including comparative genome analyses, studies of cyanotoxins that may cause death in wild life, and ecological studies in freshwater ecosystems. In addition to work involving staff at the unit, strains from the collection have been employed by many other groups working on various aspects of cyanobacteria.

During the period 2006 – 2010 a total of 37 original papers with one or more authors directly associated with the unit were published in peer-reviewed journals of medium to good impact. Twenty two of these papers have internal scientists as first and/or senior author(s). In addition, three book chapters, a French publication on water management, and 10 proceedings associated with oral presentions at international meetings were published during the period. A total of 60 oral communications and 37 poster presentations were presented at international and national meetings during the 5-year period. Two post-doctoral fellows, three Ph.D. students, and four master of science students were involved in the research during 2006 - 2010. As of December 2010 only the Head of the collection (40 years-old, Ingeneer IP, h-index 9, 15 publications) is engaged in research.

The unit has had collaborations with several research groups in France and in other countries, and nine scientists from Germany, the USA, and France visited the unit for short periods.

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

Current and previous scientists from the unit have given 11 invited presentations at international symposia and workshops testifying to their international reputation.

During the 5-year period, the unit hosted three French post-docs for 1½ – 3 years and nine short-term visiting scientists, six of whom were from Germany and the USA. The unit has also obtained eight research grants of which two will be active beyond 2010 (Contrat UE and ANR).

Strains from the collection are distributed to research groups worldwide on a semi-commercial basis. Approximately 200 strains are sold each year. A database search identifies more than 5400 research publications that employed strains from this collection and there are currently 77 ongoing genome projects that include these strains.

The collection has been an important source of material for the international cyanobacterium research community and has actively contributed to the area with important studies of the taxonomy, evolution, diversity, ecology and physiology of this important group of environmental bacteria. The unit is serving as a reference center for this phylum of bacteria.

- Appreciation on the scientific strategy and the project

The head of the unit has plans for ongoing research, mainly as a partner in collaborative studies due to the very limited resources of the unit.

The phylogenetic and taxonomic work performed within the unit combined with data generated in current genome sequencing studies performed by others on strains from the collection will serve as an important basis for ongoing metagenomic studies on environmental ecosystems.

- Conclusion :

  – Summary

The Cyanobacteria collection is a unique collection of ~ 750 environmental strains that have been an important source for research within the unit as well as internationally. Within a 5-year period the staff, temporary post-doctoral fellows, PhD and MSc students, often in collaboration with scientists at other institutions in France and in other countries, successfully employed the collection in studies of the diversity, ecology and phsyiology of cyanobacteria, which were reported in a relatively large number of original publications and book chapters. The unit obtained good external finnacial support and have two grants that are active beyond 2010. Lately, several key staff members retired and the current head is the only scientist remaining.

  – Strengths and opportunities

Given the limited ressources, the team leader should be commended for doing the best possible at maintaining this collection and at establishing collaborations with other group.

This is an important collection with significant research potential that warrants to be maintained somewhere.

Weaknesses and threats

After the retirement of several key staff members and the ensuing reorganization the group is too small to perform high quality and independent hypothesis-driven research.

Full exploitation of the potential of the collection would require significant investments in terms of personnel and laboratory space which, with the overall priorities of the Pasteur institute, is not recommended.

  – Recommendations

The committee did not find compelling arguments for the Pasteur Institute to remain the host of this important collection. Therefore, it is recommended to close the unit and to identify an alternative host for the collection.

Title of the team : Helicobacter Pathogenesis

Name of the team or project leader: Ms. Hilde DE REUSE

- Staff members

	Future
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)	2
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2
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 2.8 of the application file)	
N7: Number of staff members with a HDR or a similar grade	2

This is a provisional unit created in January 2008. All the xternal reviews concerning the activity of this unit were very positive. If the unit is transformed into a full unit by the end of the provisional period this team will apply to become part of the URA2172 CNRS superstructure. The new team leader (51 year-old, CL-IP, h-index 14, 46 publications) took over the *Helicobacter pylori* (Hp) unit after the retirement of the former unit leader (A. Labigne). Another permanent scientist is full part of the unit (51 year-old, Chargé IP, h-index 9, 31 publications), as well as a MCUPH from Cochin Hospital for 10% of her time.

- Appreciation on the results

Both permanent scientists of the IP unit "Helicobacter pathogenesis" have established several new lines of original research, concentrating on Ni-metabolism and Ni-mediated gene regulation, nitrogen metabolism (complex interplay of urea, Asn/Asp, Gln/glu and ammonia), RNA metabolism and genotoxic host response to Hp infection and gastric cancer. With these activities the group has found an original and interesting research niche in the very competitive field of Hp research and gained a clear and internationally highly recognized research profile within a relatively short time.

The team has published several first/last author papers (20 over the period 2008-2010) in high-ranking microbiology journals such as Mol Microbiol (2007), Plos One (2008), Mol Cell Proteomics (2008), Appl Environ Microbiol (2008), Infection Immunity (2008, 2010), J. Bact (2010), BMC Genomics (2010) and BMC Microbiol (2010). The team leader is also last author of an excellent EMBO paper and has also been invited to write reviews in FEMS Immunol Med Microbiol (2007) and Trends Biochem Sci (2008). One of the permanent scientist is co-inventor of a patent.

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

Both permnanet scientists have been invited to large numbers of national and international conferences (including Gordon conference in 2007) and symposia, in part as key speaker. They were also quite successful in being part of various national and international cooperations and in obtaining financial support by national (PTR, ANR) and European grants (EU Network of Excellence Europathogenomics). The funds raised by the two permanent scientists since 2005 exceeds 600 k€. In particular, the team has a strong collaborations with a Structural Biology group in Grenoble and several European and American Hp groups.

- Appreciation on the scientific strategy and the project

The research activity with the unit is clearly distinguishable in two main streams headed by each of the permanent scientist. They both provided a clear and convincing research programme for the period 2006-2010. Emphasis will be put on the interplay of metabolism and virulence in Hp infection (leader of the unit) and the genotoxic host responses to Hp infection and Hp-mediated gastric cancer (other permanent scientist). The distribution of the group memebrs on these two projects at the moment is 5 to 3, respectively. Among the scientific activities performed by the unit leader, the work on Ni-metabolism and Ni-dependent gene expression are cutting edge projects, but also the projects on ammonia trafficking and ammonia fluxes in Hp, as well as the studies on RNA stability acting as adaptive regulation of gene expression in Hp are interesting and of high quality.

- Conclusion:

  - Summary

This is an excellent unit belonging to the leading groups in the field of Helicobacter pylori research. If the provisional unit is confirmed into a full unit, it will significantly strengthen the scientific impact of the new proposed CNRS URA2172 " Functional and Molecular Microbiology".

  - Strengths and opportunities

The work on nickel and nitrogen metabolism by the leader of the unit is excellent.

The project developed by the other permanenet scientist on the epigenetic effects caused by Hp infection resulting in reduced USF1 and USF2 expression is also of high quality with promising developments that merit further extensive investigation.

  - Weaknesses and threats

The work on mitochondrial genome mutations and their possible influence on the development of gastric neoplasia is interesting but presently in a still rather speculative state as a convincing molecular basis for the possible correlation of the increased mutations in mitochondrial DNA and cancer development is lacking.

The diversity in the projects should be proportional to the size of the group, and the unit should make sure the focus is put on the most promising objectives.

  - Recommendations

Given its recent and highly relevant contributions and the excellent quality of most of the projects, the scientific committee feels that this provisional unit deserves to be converted into a permanent unit and possibly allowed to increase in size to remain competitive in its research activities.

The team should be encouraged to look also for a possible correlation between special food supply (e.g. diets rich in Ni and/or the four essential amino acids) and the development of acute Hp infections and Hp-mediated cancer.

The research addresses very important metabolic aspects (nickel and nitrogen) in Helicobacter pylori. This is quite unique and could clearly be identified as the one specific niche of this unit.

Title of the team : Bacterial Membranes

Name of the team or project leader: Ms. Cecile WANDERSMAN

- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	5
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3
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 2.8 of the application file)	
N7: Number of staff members with a HDR or a similar grade	4

The unit is currently led by a scientist with international visibility (CL-IP, 62 year-old, h-index 34, 86 publications). The unit was created in 1999 arrives at the term of 12 years mandate at the end of 2010. Although the team leader is approaching retirement age, she has expressed the desire of leading the unit for another 4 years and to retire at 70 (in 2018). There are four other permanent scientists with variable levels of expertise in this unit. One is a DR2-CNRS (55 years-old, h-index 27, 55 publications). He has shown he was an essential component in the scientific development of the unit, but has not yet shown leadership quality. Another scientist, who joined the unit in 2004 after closure of M. Hofnung unit, is going to retire (DR2-INSERM, 64 years-old, h-index 24, 70 publications). However, his research activity on ABC transporters will be taken over by a younger scientist who joined the unit in 2006 (46 years-old, Chargé IP, h-index 9). It should be noted that this scientist doe not have a HDR yet. Finally, another permanent scientist (63 years old, h-index 24, 78 publications) has temporarily joined the unit in 2009 after closure of Antoine Danchin unit. There are also two post-docs, three PhD students, one M2 and one L3 student. Other staff members are an engineer, a technician, and one half time secretary.

- Appreciation on the results

The group leader is highly accomplished with an international reputation. Her research group is highly focused and productive. Her group's work on type 1 secretion systems and ABC transporters (efflux pumps) is of the highest quality. We heard, for example, recently, they were the first to isolate and study the first full length ABC transporter from *Staphylococcus*. They continue to make fundamental discoveries using the *Serratia marcescens* hemophore to study structure and function of ABC transporter interactions using a variety of technologies. She has expanded her work recently to the study of heme trafficking and metabolism. We heard about the continuing work on the biology and molecular biology of the heme acquisition system (Has) from *S. marcescens* (type I secretion of the hemophore HasA), which was discovered by the team leader in the 1990's. HasA has no N-terminal signal peptide and when secreted, scavenges extracellular heme and then binds the HasR receptor. The group has many collaborations to study structure and function of the Has system. The biochemical and structural work provided the basis to study heme binding, heme transfer, and heme dependent signal transduction via the heme receptor using state of the art technologies and modeling (including molecular dynamics). The biology of heme acquisition is fascinating. For example, we heard a summary of the work of a PhD student on the genetics and biochemistry of how *H. influenzae* extracts heme from hemopexin. In 2008, the group made a fundamental discovery of deferrochelation, an activity to remove iron without cleaving heme (breaking the tetrapyrole ring). This new activity is found in diverse gram-positive and gram-negative microorganisms and is likely to have a broad impact.

Overall, in the last year major discoveries have been made by this group and have been published in high profile journals. It includes the structure of the heme-hemophore-receptor complex (*S. marcescens*) (PNAS 2009);

deferrochelation (*S. aureus*) which is extracting the iron from the heme without breaking the backbone (PNAS 2009); transport via ABC devoid of TM and role in macrolide extrusion (*S. pneumoniae*) (MsrD and MefE) (JBC 2008); multiple signals in T1SS-dependent protein (J Bact, 2010). This group produced 26 publications since 2006.

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

The group leader lists 86 publications with an h-index of 34. Her publications are in journals of high quality and visibility. She is invited to speak at meetings (including Gordon research Conference on tetrapyrols) and write reviews. She leads her group with energy and enthusiasm and, it is my opinion from listening to the talks, that she provides positive mentoring to develop her younger scientists in their careers. Her main collaborator for many years has also an impressive track record (h-index 27, 55 publications) and although he has not demonstrated a charismatic leadership, his scientific quality and contribution to the international quality of the research in this unit is not questionable. The youngest scientist (h-index 9) in the unit needs to improve his track record and needs to obtain a HDR in the near future.

The funds raised by this group are not exceptional but we can identify 2 active ANR grants.

- Appreciation on the scientific strategy and the project

The unit leader proposes four concise research programs: two to be headed by her and two by the younger scientific staff in the unit. Her first program focuses on protein secretion. Here she will construct more efficient secretion vectors in hopes of improving production and purification. This was only briefly presented and seems to be of modest importance. The second is more exciting and detailed. Here she will study heme deferrochelation in E. coli and S. aureus. This reaction removes iron from heme in a completely novel reaction. Biochemistry and genetic approaches are proposed that are technically demanding but have a high probability of success and may reveal more novel biochemistry. This second project will be the focus of her new proposed group and is highly relevant and well focused.

The team leader has proposed to form a new smaller group consisting of herself, the IP scientist coming from A. Danchin unit and an engineer. This scenario is ok but may not be optimal for the continuation of the current science. Indeed, we may understand that the group leader wish to give more visibility and independent research activity to the younger members of her staff, but one wonders about the merits of breaking up this highly productive and innovative group. In particular we have no real evidences that one of these younger scientists demonstrated a real leadership. Therefore, the committee makes the alternative recommendation that this group be kept together as long as the team leader is here.

- Conclusion :

  – Summary

The activity is very broad but well organized between team members into four research themes. These are Type I secretion systems (T1SSs), Heme uptake, Heme transport and metabolism, phylogeny and function of ABC transporters. Each research themes includes original and innovative aspects, both in terms of intellectual concepts and in experimental approaches. This excellent research activity results from pioneering work by the group leader, and though the members of the group have shown their scientific excellence none of them can really take over the leadership. The historical research activity in the unit is the study of T1SS in bacteria and it developed into iron uptake and metabolism essentially after the discovery of a T1SS involved in secretion of a hemophore (HasA). In any cases the quality of the Science has always been kept at international level and shall continue to be so as far as the group is kept together.

  – Strengths and opportunities

- The team is headed by a highly accomplished scientist with an excellent track record.

- The PI is a strong, charismatic leader.

- The PI has provided positive mentoring for members of her group.

- The team has made a discovery of major importance during the past 4 years.

– Weaknesses and threats

- If the group is reduced in size, the synergy, innovation and discovery within the unit may not continue.

- The young scientist proposing the project on functional studies of VgaS and MsrD in E. coli, should probably narrow his activity and avoid proposing a project with scarce perspectives and unfocus. He will also need to improve his track record.

- In the unit, tthere are no other scientists than the group leader with a potential for charismatic leadership.

– Recommendations

- The unit is at the end of its 12 year mandate. The team leader has proposed to downsize her group and should be allowed to do so if she really wants. However, it is not clear whether any other scientist within the team will have the strength and the capability to maintain the high visibility of this unit. Under these circumstances, the scientific committee recommends that the unit be renewed and kept in the same format. Moreover, the scientific committee recommends that the current head of unit be confirmed in her leadership.

5 • Appreciation team by team (not belonging to URA 2172)

Title of the team : Fungi Culture Collection

Name of the team or project leader: M. PAPIEROK

- Staff members

	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	
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 (Forms 2.2, 2.4 and 2.7 of the application file)	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3.1
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 2.8 of the application file)	
N7: Number of staff members with a HDR or a similar grade	

- Appreciation on the results

The Fungi Culture Collection is not a typical research unit, although there are some research activities. Its main tasks consists of production, characterization, preservation, control, and distribution of fungal strains, as well as expansion of the collection with new original isolates. The collection, which includes more than 2700 strains, became certified according to the ISO 9001:2000 standard in 2009. It is part of the Pasteur Institute Biological Ressource Center (CRBIP). The unit distributes and identifies cultures on request from research laboratories in universities and industry, but is not a recognized national reference center. The unit performs research directly linked to the utilization and expansion of the collection. The research activities are mainly directed to develop new molecular markers for fungi and to investigate entomopathogenic fungi such as fungi parasitizing forest insects in temperate areas and tropical areas. A third function of the collection is teaching and training.

Within the last 5 years a total of 6 publications are listed, one of which describes the collection and the remaining are chapters in books. None are based on original research or are published in peer-reviewed journals. There are no research students or post-doctoral fellows associated with the unit.

The collection distributed 450-500 cultures during the last 5-year period.

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

The unit received minor national and European grants, mainly as a partner of the Centre de Ressources Biologiques de l'Institut Pasteur (CRBIP).

*As part of CRBIP, the unit is part of the European Consortium of Microbial Resourve Centres under the 7th Framework Programme, Capacities Specific Programme, Research Infrastrucure.

The documented research activity is focused on maintenance and expansion of the collection.

- Appreciation on the scientific strategy and the project

Activities are continued to maintain the quality of the collection. As part of the EU network, research aimed at the development of molecular markers for yeast and filamentous fungi to improve classification and identification is ongoing. In addition, taxonomic studies on entomopathogenic fungi from forest ecosystems are planned.

- Conclusion :

  - Summary

The Fungi Culture Collection is not a typical research unit, and as such has a very limited added value to the Microbiology department or Institut Pasteur scientific output. The emphasis on entomopathogenic fungi might also not appear most appropriate for the department.

  - Strengths and opportunities

This is a large, though not unique, collection of fungi that distributed cultures to research groups in France and other countries on request and on a semi-commercial basis. The collection is well organized and presented on its homepage.

  - Weaknesses and threats

The group members are close to retirement.

The collection is not a national reference center for fungi, which is available elsewhere in Paris.

  - Recommendations

The scientific committee did not find any compelling argument for the Pasteur Institute to remain the host of this collection. Therefore, it is recommended to close the unit and, if possible, to identify an alternative host for the collection.

Title of the team : Antibacterial Agents

Name of the team or project leader: M. Patrice COURVALIN

- Staff members

	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1
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 (Forms 2.2, 2.4 and 2.7 of the application file)	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4
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 2.8 of the application file)	
N7: Number of staff members with a HDR or a similar grade	3

This unit is headed by an internationally renowned scientist with an outstanding track record (Prof – IP, h-index 74, more than 300 publications). The team leader wil retire in 2014, whereas the unit is due to be at the term of its current mandate by the end of 2012. Three other permanent scientists are part of the unit, a DR2-CNRS (63 years old, h-index 18, 38 publications), an assistant Professor IP (57 years old, h-index 13, 30 Publications) and an associate professor IP (60 years old, h-index 18, 40 publications). None of the three permanent scientists is a potential successor for the ciurrent leader. There are also 2 assistants for the unit, 1 engineer, 1 technician and a pharmacy resident together with two persons in charge of the sterilization and media service.

- Appreciation on the results

The team leader has a stellar track record over many years for his research on antibiotic resistance (AR). These studies have involved investigation of both nosocomial and community acquired bacterial pathogens. There has been a major emphasis on AR in beta lactams and glycopeptides. The major contributions have centred around the mechanisms of AR and multiple examples of all major modes of AR have been described: (i) decreased drug uptake; (ii) modification of enzymatic degradation; (iii) altered drug targets; (iv) intracellular antibiotic sequestration. This research has driven the development of a range of diagnostic laboratory assays in the associated Reference laboratory. The research has focused much less on the origins, evolution and spread of AR but recent work on how bacteria regulate their AR phenotype, as distinct from having a constitutive phenotype, provides an admirable example of research aimed at understanding the fitness consequences of AR and its implication for the spread of these bacteria. There has also been impressive research on the development of a mammalian cell system for DNA and protein transfer with important IP that could have important applications in the development of therapeutic and vaccine vectors.

During the 2006-2010 period, the team has published 50 papers, many of them in antibiotics-related journals such as AAC, and few in higher impact factor journals such as a recent publication in PNAS about vancomycin resistance.

- 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 given over 50 conferences since 2006 and including international conferences for the FEMS, IUMS, Keystone or ICAAC. The team leader is also fellow of the French National academy of technologies, of the European academy of clinical microbiology and infectious disease, and chevalier de la legion d'honneur since 2009. The team leader has an impressive network of national and international collaborators.

The team leader is also in the editorial board of several journals and member of several committees on public health and antimicrobial resistance.

Finally the team leader is inventor on 4 patents.

The funds raised by the team include ANR (MIME – 2007/2010, 135k€), VLM (2009/2010, 55 k€), European consortium FP6 and FP7 (for a total over 650 k€). It also includes the programme NOSOBIO associating PMEs and addressing the problem of nosocomial infections.

- Appreciation on the scientific strategy and the project

In terms of the future, the team leader retires in 2014 and his Unit reaches its full term in December 2012. Sadly, the committee could not currently identify any appropriate Pasteur scientists who could be successors to the current team leader, an example of a prevalent problem within the Department of Microbiology because of the imminent retirement of several senior and prestigious scientists (the so called "Aging Problem"). The committee were unanimous in their view that this area of research is a most important component of the Department's portfolio of research subjects and ought to be continued in the future. For this to occur, it seems inevitable that immediate and urgent consideration be given to recruitment of an internationally recognised scientist with or without a medical degree. Ideally, such an appointment should build on, but be different from, the heritage of the team leader (research on mechanisms of AR) by focusing on aspects such as the origins, evolution and spread of AR -- to cite just a few of the potential areas that could be considered. Thus, there is enormous scope for an inspired, exciting appointment that would be of great relevance and importance to the future of the Pasteur's Department of Microbiology and its other Departments.

- Conclusion :

  - Summary

This is a laboratory with an international profile and a charismatic leader with an outstanding track record. The unit is due to close by the end of 2012 and the team leader will retire in 2014. The research activity on antibiotic resistance is certainly an area that should be covered by the Pasteur Institute. Obviously, this activity should be maintained but the focus may be changed and could address spread and evolution of resistance rather than mechanisms. Also the efforts on identification of new compounds could be an interesting area of investigation and research on Streptomyces could be linked to the activity of this unit. These thoughts will be important to consider after the retirement of the current leader since the next leader is likely to come from outside Pasteur, no one in the unit being in a position to take over and maintain the research standard and international visibility of the unit.

  - Strengths and opportunities

This team is working in a very important field for Microbiology.

The recent work on vancomycin resistance has a very strong impact.

The team leader has a quite unique track record.

  - Weaknesses and threats

There is no obvious alternative to take over the head of the unit after the retirement of the current leader.

Alternative approaches could be considered to investigate the field of antimicrobal resistance.

– Recommendations

The scientific committee feels that the research on antibiotic biochemistry and the evolution and dissemination of resistance should definitively be maintained at the Pasteur Institute. Proactive action should be taken now to implement this decision. It is also the general feeling that the Pasteur Institute has the responsibility to contribute reference ressources in the field of antibiotic resistance. What the focus of the reference activity depends very much of the future of this research activity at the Pasteur Institute. The final decision on maintaining this unit and this research activity will thus be very much dependent on the ability of Pasteur Institute to recruite a credible altrnative to the current leader.

Title of the team : CIP

Name of the team or project leader: M. BIZET

- Staff members

	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	
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 (Forms 2.2, 2.4 and 2.7 of the application file)	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	8
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 2.8 of the application file)	
N7: Number of staff members with a HDR or a similar grade	1

- Appreciation on the results

The functions of CIP were defined as “enrichment and preservation of bacterail strains, edition of a regularly updated catalogue, combined with research activities on taxonomy and preservation of bacterial strains”. The collection includes nearly 12000 strains presented in a well-functioning on-line catalogue. The strains are distributed to researchers nationally and internationally on request and on a semi-commercial basis. Apart from the production of new vials and maintenance of the collection in two different ways and stored in two different localities, the activities include extensive quality control and constant monitoring and application of taxonomic changes of bacteria included in the collection. In order to take advantage of the larger collections of bacterial genera in the collection, the unit is establishing and expanding research on taxonomy, phylogeny, and typing in collaboration with scientists within and outside the Pasteur Institute.

During the 5-year period eight publications include staff of CIP as authors, three of these as first and/or senior author. The publications describe new taxa, taxonomic changes of existing taxa, or deal with quality control of bacterial identification methods.

CIP has served as a source of bacterial strains for studies performed by scientists at the Pasteur Institute and has distributed strains on request from external scientists in France and other countries and is a highly appreciated resource. More than 3200 strains are distributed each year. The head of CIP is co-coordinating the European Consortium of Microbial Resource Centres, which is a project under the 7th EU framework. It is expected that this activity will enable the development of new partnerships with public institutes in the field of biodiversity, and is expected to facilitate revenue-generating partnerships with the commercial sector.

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

Three grants were obtained during the period, two of them national and one European (see above).

Staff of CIP have been coordinating national consortia that were instrumental in developeing software for management of collections, and evaluated new quality markers and alternative methods for preservation of microbial strains. The head of CIP is currently co-coordinating the European Consortium of Microbial Resource Centres, which is focusing on the sustained collection facilities within Europe and relevant teaching activities. Members of the staff gave oral and poster presentations at several congresses and workshops.

CIP has fulfilled its functions as defined by the Pasteur Institute and is an important resource for microbiologists within and outside the institute. Research activities are ongoing and an increasing proportion of the time is being spent on research.

- Appreciation on the scientific strategy and the project

There are interesting and valid research plans that include development of new ways to store microorganisms and DNA, exploration of new means to identify microorgansisms, including quality control of identification by mass spectrometry, phylogenetic studies, taxonomic studies on seleted bacterial taxa, and studies on the emergence and diversification of selected pathogens over time.

The unit successfully changed priorities with increasing focus on research activities.

The research plans for the future in collaboration with other staff within the Pasteur institute are orginal and may potentially generate important results.

- Conclusion :

– Summary

CIP is an internationally recognized resource for microbial research. The collection maintains nearly 12000 strains and distributes more than 3200 strains annually to scientists inside and outside the Pasteur institute. The unit plays an important role in national and European consortia and is currently co-coordinating a consortia supported by the EU. The unit performs some, though limited research due to the main activities and the need for constant maintenance and control of the collection. However, an increasing part of the time is being used on research activities, mainly in collaboration with other scientists within and outside the Pasteur institute. There are interesting and valid plans for research activities for the next 4-year period.

– Strengths and opportunities

CIP is a well recognized collection that has distributed a large number of strains worldwide and that has been very useful to the international microbiology community.

The management of the collection is very professional in terms of security, quality control, and presentation to its users, and the current head shows dedication, entusiasm, and initiative.

The unit has obtained several grants and is part of an european consortium.

– Weaknesses and threats

Collections like CIP cannot be run in a commercially feasible manner.

Due to the limited scientific staff, research activities are to a high degree dependent on collaborations with other scientists internally or outside the Pasteur Institute.

– Recommendations

Institutions like the Pasteur Institute should definitively contribute to the maintainance of important collections such as this one. However, the decision to maintain or not this particular collection at the Pasteur Institute is difficult to make without knowing the costs and the relative merits for the Pasteur Institute and the microbiology community. In this context, the scientific committee suggests closing the unit and, if possible, to identify an alternative host for the collection.

Title of the team : Anaerobe Bacteria and Toxins

Name of the team or project leader: M. Michel POPOFF

- Staff members

	Future
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 (Forms 2.2, 2.4 and 2.7 of the application file)	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	6
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 2.8 of the application file)	
N7: Number of staff members with a HDR or a similar grade	2

This unit was created in 2002 and is close to the end of its second 4-year mandate. The team includes two sub-groups, one of which is the National Reference Centre (CNR) for anaerobes. In addition to the head of the unit (CL-IP, 61 years-old, 171 publications) a permanent scientist is involved in the botulism and toxins research (CL-IP, 54 years old, 35 publications) and another permanent scientist is directly involved in the CNR management (chargé IP, 57 years old, 36 publications). The Pasteur Institute has decided this unit to include up to 12 members. This is sometimes problematic, in particular to accommodate temporary post-docs. It should be noted that in 2009 another subgroup was temporarily part of the unit, but the two permanent scientists have joined since a new unit created in October 2010 (Anaerobe pathogenesis).

- Appreciation on the results

The research is on genetics of Clostridia and has strong emphasis on clostridial toxins. Main work is on toxins, botulism, and reference activities at CNR. The research is very relevant in particular on the toxin part, where the group has a unique position in the world. The research is very focused and therefore sometimes a bit narrow, sometimes lacking links of toxin production to basic physiology of Clostridia. Also a FP7 EU grant was obtained, extending the international network.

Main Research programmes are:

- Botulism (multidisciplinary with studies on BoNT). Interactions with host cells, regulation of toxinogenesis.

- Large clostridial toxins (actin cytoskeleton, cell signalling, use of mice, neurotransmitter release etc.)

- Characterization of Clostridial pore forming toxins (necrosis, channel forming-domain studies, cell membrane micro-domains).

- Entry of binary toxins into cells.

- Characterization of new toxins.

- Research linked to CNR (taxonomy, detection, antibodies).

During the past four years, the team has published several first/last author papers in the following journals: Journal of Applied Microbiology (2009), Cell Microbiol (2010a, 2010b,2009a, 2009b, 2008a, 2008b), Toxicon (2010), Plos One (2010a, 2008), J Clin Microbiol (2008), FEBS letter (2007), Am J Pathol (2007), Biol Cell (2006a, 2006b). Another paper is in revision in Plos Pathogen.

The team leader was also invited to write reviews in journals such as Future Microbiol (2009) and BBA (2009). The team members have also written two books and a few book chapters.

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

The group leader is regularly invitated for talks on high ranking international meetings. The other scientist has a more modest reputation in this respect.

The group is successful in fund acquisition, e.g. INSERM, CNRS, DGA, IMASSA. The team has also a strong collaboration with Sanofi Pasteur and benefits from grants from the French army.

There are few international programs in which the group participates e.g. FP7 EU grant. However, the group does not seem to have a very broad international network

In conclusion, a good funding obtained, especially in France, and good Socio-economic partnerships with French Army and Sanofi.

- Appreciation on the scientific strategy and the project

The work on toxins and Clostridia is very relevant, clearly visible and recognized within the scientific (toxin) community, and fits very well at Inst. Pasteur. Another 4 years period is justified in view of the well organized relevant research lines. The subprograms are state of the art and sometimes cutting edge. Real top publications (Cell, Science, Nature, EMBO J, PNAS, etc.) are lacking. Allocation of resources is done very well, in particular by the group leader. The originality of the research could be further improved when more links are considered in studying the regulation of toxin production (also at the single cell level), the metabolic and physiological effects and effects on regulatory networks.

- Conclusion:

  - Summary

A well organized and focused Unit with several very strong research lines that are sometimes interlinked. The Unit is 12 ETM awarded, which is sometimes not sufficient to accommodate temporary scientists e.g. employed as postdoc. The work could be extended a bit more into clostridial physiology related to toxin production, e.g. by also employing single cell studies and genomics/bioinformatics approaches.

  - Strengths and opportunities

The research activity is solid

The team leader has a very good publication record

The team has developed a coherent program and focused projects

The publication record is good with 10-11 publications a year in very good journals.

  - Weaknesses and threats

The work on toxins is somewhat conventional and not always ground breaking (No publications in Top journals).

The CNR could be better utilized in the research acivities.

There is no obvious candidate to take over the unit when the team leader retires

- Recommendations

The scientific recommend that the unit should be continued for the next 4 years. However, the research could be put in a more physiological context, also on the clostridial side. Novel technologies could be integrated. A careful consideration of the future of this unit will have to be made regarding the continuation of this unit after the next 4 year period.

Title of the team : Molecular Biology of Gene in Extremophiles

Name of the team or project leader: M. Patrick FORTERRE

- 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)	5
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1
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 2.8 of the application file)	
N7: Number of staff members with a HDR or a similar grade	4

Current members of the unit include five staff scientists (1 Professor, 1 Associate Professor, and 3 Assistant Professors) and two technicians. The group leader (Professor Paris XI, 61 years old, about 200 publications) is heading this unit since January 2004. The unit is thus at the end of its second mandate. The leader joined Pasteur together with two other permanent scientists (62 years old, CL-IP, h-index 20, 90 publications; and MCU Paris 6, 50 years old, h-index 8, 23 publications). Other scientists joined the unit in 2005 (Chargé IP, 41 years old, h-index 15, 35 publications), and in 2006 (Chargé IP, 43 years old, h-index 8, 16 publications).

- Appreciation on the results

This is an outstanding unit at the forefront of research on the biology and evolution of the archaea and the viruses that infect these microorganisms. The unit is composed of three groups whose themes of research are 1) viruses of the hyperthermophilic archaea, 2) phylogenomics and microbial evolution, and 3) virus/bacteria interactions in animals. The scientific production of the first two groups is excellent. The third group, which is the most recent addition to the unit, is developing model systems to explore the complexity of virus/bacteria interactions in an animal host.

For the reporting period (2006-2010), the unit has been highly productive with 69 articles and reviews published in international journals with an editorial board and 3 patents. Highlights include articles published in *Genome Biology, J Infec Dis, J Virology, Nature Reviews Microbiology (4x), PNAS, TIBS and Virology.*

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

The international visibility of the research conducted in this unit. The leader is a charismatic scientist with an outstanding track record and who headed the Department of Microbiology until December 2009.

The unit has attracted significant amount of grants from Pasteur Institute (PTR), VLM or ANR (3 grants during the period 2006-2010). One of the ANR grant is a young investigator research grant to the head of the subgroup on phylogenomics. European funding have also been obtained (Marie Curie) and a number of fellowships (Institut Pasteur, EMBO and FEMS).

The group leader is a senior member of the "Institut Universitaire de France". He has been invited to more than 20 international meetings in the last four years. The other members of the unit have also shown an active contribution to international meetings, both as speakers and organizers.

The unit has also filed 3 patents since 2006 on thermostable DNA polymerase or therapeutics use of bacteriophages.

- Appreciation on the scientific strategy and the project

The projects for the next four years build on ongoing research. Important goals include the continuation of the isolation and characterization of viruses that infect hyperthermophilic archaea; studies on the molecular mechanisms of the transcription, replication, assembly and release of archaeal viruses; phylogenomic analyses aimed at elucidating the origin of the Cyanobacteria and photosynthesis; and the development of a new model system involving the analysis of the impact of bacteriophage on the flora of the animal gut.

- Conclusion :

  - Summary

This is an international quality unit, with a leader holding an outstanding track record in his research field. The science is original and cutting edge, and so is the quality of the publications. The virus associated pyramids (VAP) is one example of striking discoveries that have been made by the unit. There are two promising young researchers in the unit. One seems already established and has found her niche (phylogenomics), the other starting a new research program that needs to demonstrate sustainability.

  - Strengths and opportunities

International class and exciting research in the field of Achea. One of the last big group in this area.

Excellent output and high quality publications.

The leader of the group on phylogenomics is young, was given relative independence and has a very high potential.

The activity of the sub-group on bacteriophages should demonstrate sustainability but is promising. The group leader should obtain his ability to supervise PhD students (HDR).

  - Weaknesses and threats

The space allocated to this team does not match the visibility of this unit and its scientific contribution.

The team leader is aging and the future of the unit should be anticipated.

  - Recommendations

The committee found no significant weakness in this unit although the sub-group working on virus/bacteria interactions in an animal host needs to demonstrate that it can maintain momentum on recently initiated projects. The committee believes that the unit request for additional space is justified by the highly specialized technical needs associated with growing hyperthermophilic archaea. In conclusion, the scientific committee recommends that the unit be extended for another 4 year period. At the end of this period, it will be important to evaluate whether the future of the unit has been considered with care, knowing that the leaders are approaching retirement age. The committee would also like to highlight the promising performance of one of the younger scientist (Chargé IP, 41 years old, h-index 15, 35 publications) in studying this very particular niche of hyperthermophilic archaea.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
DÉPARTEMENT DE MICROBIOLOGIE	A+	A+	A	A+	A+
CIP [PUGSLEY-BIZET]	Non noté	Non noté	Non noté	Non noté	Non noté
YERSINIA [PUGSLEY-CARNIEL]	A+	A	Non noté	A+	A+
ANTIBACTERIAL AGENTS [PUGSLEY-COURVALIN]	A	A+	Non noté	A	A
HELICOBACTER PATHOGENESIS [PUGSLEY-DE REUSE]	A	A	Non noté	A	A
ANAEROBE PATHOGENESIS [PUGSLEY-DUPUY]	A	B	Non noté	A+	A
MOLECULAR BIOLOGY OF GENE IN EXTREMOPHILES [PUGSLEY-FORTERRE]	A+	A+	Non noté	A+	A+
GENETICS OF BIOFILMS [PUGSLEY-GHIGO]	A+	A+	Non noté	A+	A+
BIOLOGY AND GENETICS OF BACTERIAL CELL WALL [PUGSLEY-GOMPERTS-BONECA]	A+	A+	Non noté	A+	A+
TOXINS AND BACTERIAL PATHOGENESIS [PUGSLEY-GOOSENS]	A	B	Non noté	A	A
CYANOBACTERIA COLLECTION [PUGSLEY-GUGGER]	Non noté	Non noté	Non noté	Non noté	Non noté
FUNGI CULTURE COLLECTION [PUGSLEY-PAPIEROK]	Non noté	Non noté	Non noté	Non noté	Non noté
BIOLOGY OF SPIROCHETES [PUGSLEY-PICARDEAU]	A	A+	Non noté	A	A
ANAEROBE BACTERIA AND TOXINS [PUGSLEY-POPOFF]	A	A	Non noté	A	A
MOLECULAR GENETICS [PUGSLEY-PUGSLEY]	A+	A+	Non noté	A+	A+
BIOLOGY OF GRAM-POSITIVE PATHOGENS [PUGSLEY-TRIEU-CUOT]	A+	A+	Non noté	A+	A+
BACTERIAL MEMBRANES [PUGSLEY-WANDERSMAN]	A+	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**

Institut Pasteur

Paris, le 15 avril 2011

Unité de Biologie des Bactéries
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De : **Patrick TRIEU-CUOT**

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OBJET : AERES Evaluation

To whom it may concern,

I wish to thank the AERES committee for the quality of the evaluation process.

I have no major comment to make on the reports of the Department and Research Unit.

Sincerely yours,

Patrick TRIEU-CUOT

Chef de l'Unité de Biologie des Bactéries
Pathogènes à Gram-positif

INSTITUT PASTEUR

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April 11, 2011

Dear AERES members,

We would like to thank you for your evaluation of our Research Unit.

We just want to draw to your attention that, among our well established collaborations with other leaders in the field, the long lasting and fruitful collaboration we have with the group of Mark Achtman (Cork University) would need to be cited.

With my best regards,

Elisabeth Carniel, MD, PhD,
Head of the *Yersinia* Research Unit
Director of the National Reference Laboratory and
WHO Collaborating Center for *Yersinia*

ALAIN ISRAËL
DIRECTEUR DE L'EVALUATION SCIENTIFIQUE
INSTITUT PASTEUR

Institut Pasteur

Paris, le 13 avril 2011

Unité Pathogenèse de *Helicobacter*
Département de Microbiologie
Hilde DE REUSE

AERES de Reuse, Hilde

- Title: Helicobacter Pathogenesis
- Team leader: Ms. Hilde DE REUSE

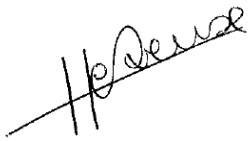
Answer to the AERES evaluation

- Weaknesses and threats

- The work on mitochondrial genome mutations and their possible influence on the development of gastric neoplasia is interesting but presently in a still rather speculative state as a convincing molecular basis for the possible correlation of the increased mutations in mitochondrial DNA and cancer development is lacking.

MtDNA mutations have been reported in a wide range of tumors and in pre-cancerous lesions as gastric pre-neoplasia, and found more frequent in *H. pylori*-positive than in *H. pylori*-negative gastric cancers. The aim of this project is not just to establish if there is a correlation between the presence of mtDNA mutations and the promotion of gastric cancer lesions. We rather want to get insights in the mechanisms implicated in the mitochondria alterations generated during *H. pylori* infection that include both mtDNA mutations and a deregulation of the mtDNA transcription machinery (as demonstrated by our recent data). We also want to understand the impact of the mitochondria alterations on the cascade of events leading from chronic gastritis to gastric cancer. Another important goal of this project is to explore the possibility to use these mitochondrial alterations as markers to detect, in the *H. pylori* infected-population, the people that present a high risk to develop gastric cancer.

Yours sincerely,



Hilde De Reuse, Head of the Unit *Helicobacter* Pathogenesis

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Institut Pasteur

G5 Biologie et Génétique
de la Paroi Bactérienne

Paris, le 8 Avril 2011

We are pleased that the committee found our work of great interest and with the general comments of the report. However, we would like to respond to the "Weaknesses and threats" reported by the committee.

- No genetic tools are currently available in the *Leptospira* model

Catherine Werts has a long lasting collaboration with the Unit of Mathieu Picardeau (for example, the J. Immunol. paper of 2009), a unit of our department that has developed such tools for saprophitic *Leptospira* and is trying to adapt them to pathogenic *Leptospira*. Hence, when available, genetic manipulation of pathogenic *Leptospira* could be achieved in collaboration with Mathieu Picardeau.

- Collaborative aspects with other units working on *Helicobacter* should be highlighted.

It was highlighted during the committee visit that we have joint lab meetings with the Unit of Hilde de Reuse that is also a spin-off of Agnès Labigne Unit. We exchange genetic tools and protocols on *Helicobacter pylori* on daily basis but these are not necessarily formal collaborative projects that should be included in an AERES report as we have distinct research topics and interests. A proof of our close interactions is our joint publication indicated in the committee report published in 2008 in Appl. Environm. Microbiol.

- The route of infection that is used to infect mice with *Leptospira* is not physiological. Currently IP but skin model will be more relevant.

We agree that more physiological models should be developed for *Leptospira* infection and a conjunctivitis model of mouse infection is being studied.

- As other groups at the Pasteur Institute, this team needs to have access to carbohydrate fine structural analysis plateform.

Although we do agree that in general the Institut Pasteur should improve its expertise in carbohydrate fine structural analysis, our group has currently all the expertise required for the fine structural analysis of peptidoglycan analysis, enzymatic synthesis of peptidoglycan fragments and even chemical synthesis in collaboration with the Unit headed by Laurence Mullard.

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G5 Biologie et Génétique de la Paroi Bactérienne

- There is a risk of too much diversity in the projects, in particular the aspects involving the host response.

As indicated by the committee, the group has two main research topics: 1) the study of peptidoglycan metabolism using *H. pylori* as a model, 2) the role of cell wall, and in particular, the peptidoglycan in host-microbe interactions. The first one is focused on *H. pylori*. The second topic can not be focused on one single bacterium as it would led to a reductionist view on how different pathogens manipulate the host response. Each bacterium has evolved its own strategy. In contrast, we focus in our group on *H. pylori* and *Leptospira*, while other pathogens have been always studied in collaboration due to our own lack of expertise and of manpower. We have been very successful in the past even without the support of a group. Hence, we believe that today with a group of 7-8 full time researchers that this particular threat has rather decreased instead.

Yours sincerely,

Ivo Gomperts Boneca

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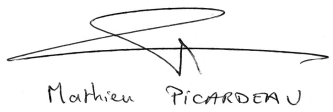
Mathieu Picardeau
Courriel : mathieu.picardeau@pasteur.fr

Paris, le 14 avril 2011

OBJET : *Commentaires concernant l'évaluation AERES de l'Unité.*

Je, soussigné Mathieu Picardeau, responsable de l'Unité de Biologie des Spirochètes, n'ai aucun commentaire à apporter au rapport de l'AERES concernant l'Unité de Biologie des Spirochètes.



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