Département infection et épidémiologie

Rapport Hcéres

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

Research Units Department

AERES report on unit:

Infection and Epidemiology Department

Under the supervision of the following institutions and research bodies:

Pasteur Institute

December 2011

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

Section des Unités de recherche

Le Président de l'AERES

Didier Houssin

Section des Unités de recherche

Le Directeur

Pierre Glaudes

Unit

Name of unit:	Infection and Epidemiology Department
Acronym of unit:	
Label requested:	
Present no.:	
Name of Director (2009-2012):	Ms Françoise DROMER
Name of project leader (2013-2017):	

Members of the committee of experts

Chair:	Ms Sophie de BENTZMANN, Marseille
Experts:	Mr Mario CLERICI, Milano, Italy
	Mr Esteban DOMINGO, Madrid, Spain
	Mr Jörg HACKER, Halle, Germany
	Mr Laurent KAISER, Genève, Switzerland
	Mr Robin MAY, Birmingham, UK
	Mr Guillaume MONNERET, Lyon
	Mr Philippe MOREILLON, Lausanne, Switzerland
	Ms Anna Paola RIZZOLI, Trento, Italy
	Mr Thierry NAAS, Paris (Inserm)
	Mr Marc STRUELENS, Stockholm, Sweden
	Mr David SIBLEY, St Louis, USA
	Mr Christoph TANG, London, UK

Representatives present during the visit

Scientific Delegate representing AERES:

Mr Pierre LEGRAIN

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

Mr Tony PUGSLEY, Pasteur Institute

Report

1 • Introduction

Date and conduct of visit:

The visit has been achieved over three days at the Pasteur Institute. It started on the 5th of December with a general presentation of the missions of the AERES committee during the visit given by Pierre LEGRAIN, the scientific presentation of the Department (achievements for the past period and goals for the future) given by Ms Françoise DROMER, head of the Department in front of all Department members. Then, the committee was split into two sub committees for team by team audiences, audiences which had been spread out up to the 6th of December noon. Each audience has been organized as a presentation given by the team leader alone or in association with several permanent members of the team, followed by exchanges with the unit members on scientific aspects but also on other aspects raised. Additionally, members of the committee have been split on three groups for each staff college audience (Technician and Engineers ; PhD students and post doctoral fellows ; permanent scientists), meetings which were included on the 5th of December before starting the afternoon audiences. A global meeting with team leaders was organized at lunch on the 6th December where members of the committee and team leaders have exchanged informally as well. The committee has met for a global in camera meeting in which evaluation has been completed all together.

History and geographical location of the unit, and overall description of its field and activities:

The Department of Infection & Epidemiology, one of the 10 research departments of the Pasteur Institute, was created in 2005, just before the last evaluation, from units in former departments of "Molecular Medicine" and "Ecosystems and Epidemiology of Infectious Diseases". During the 2007-2011 term, three research units closed because of retirement or move out of the Campus. Six new research groups were created since 2008; in 2008, the junior group "Microbes and Host barriers" (E11, M. Lecuit) and the "Pharmacoepidemiology of Infectious Diseases" unit (E9, D. Guillemot); in 2009 the "Invasive Bacterial infections" unit that accommodates the National Reference Center on Neisseria (E14, MK Taha); and in 2010 two research units, the "Enteric Bacterial Pathogens" unit that accommodates 3 National Reference Centers (NRC, Salmonella, E. coli/Shigella, Vibrio) (E16, FX Weill) and the "Human Histopathology and Animal Models" unit (E5, F. Chrétien). The Department includes 15 research units, one junior group (E11), one laboratory dedicated to emergency situations (E12), one core facility (associated to E2), nine National Reference Centers (in E1, E6, E10, E14, E16), and a reference collection of arthropod vectors (in E13). The 16 entities are distributed on the Campus over nine buildings.

This department Infection and Epidemiology is gathering teams around a common concept which has been defined as following a strong public Health dealing with Infectious diseases and Epidemiology and which feed basic science research defined as based on host-pathogen interaction.

Management team:

Francoise DROMER (Team leader of E6) is heading this department together with Michel CHIGNARD (Team leader of E4) since 2010 with a board including the heads of all units/laboratories/facility and the director of the CNRS URA3012 (all permanent members of the council), as well as elected representatives of each category of personnel. This board meets 4 times a year to discuss scientific and/or administrative matters. The Department head influences decisions on new equipment for the Campus, coordinates the scientific animation of the Department, and identifies potential new recruitment for the Department, and proposes new scientific strategies to the Direction, while the Scientific Council of the institute decides on creating and closing research units.

Unit workforce:

This Department includes specific structures : the presence within Teams of NRCs (9 NRC in 6 different teams), an integrated team with core facilities missions for emergency situations (CIBU, Team 12) as well as a team with platform missions in histopathology of animal models (Team 5).

Workforce	**Number** on 30/06/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	10 [6]	13.5 [8]	8
N2: EPST or EPIC researchers	11	10	7
N3: Other professors and researchers	36 [25]	35 [28]	32
N4: Engineers, technicians and administrative staff *on a permanent position	85 [39]	82 [35]	
N5: Engineers, technicians and administrative staff * on a non-permanent position	8 [5]		
N6: Postdoctoral students having spent at least 12 months in the unit	38		
N7: Doctoral students	42		
N8: PhD defended	34		
N9: Number of Habilitations to Direct Research (HDR) defended	14		
N10: People habilitated to direct research or similar	30	34	
TOTAL N1 to N7	**230** [87]	**140** [81]	**47**

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

2 • Assessment of the unit

Overall opinion on the unit:

This department Infection and Epidemiology is gathering 16 teams around a common concept which has been defined as following a strong public Health activity (11 teams /16 are involved in such a concept) dealing with Infectious diseases and Epidemiology and which feed a basic science defined as based on host-pathogen interaction. This Department has a unique strength that is the presence within Teams of NRC (9 NRC in 6 different teams). This includes activities of research and expertises in viral fungal and bacterial diseases. This is indeed a reality and the department is truly trying to feed basic research with real life issues. It has also a very strong teaching and training activity, denoting of its intrinsic expertises. This is from this overall description a very heterogeneous department with a global very good level of publications and a very good level of recognition of the scientists in their field. On the other side due to diversity of subjects, it appears that connections between teams are not as high as could be expected, highly variable from one team to another and that connections with other departments should also be reinforced in particular for “isolated” small teams which could benefit from the potential of teams present in other departments in IP. This is a global feeling which thus generates a highly variable research level from one team to another and cannot be generalized to the Department as a whole. Therefore the heterogeneity of the department is also illustrated by the unequal qualities of the teams.

Strengths and opportunities:

The strong connection of teams with NRC, WHO and the International network of IP is a very strong aspect of this department thus rendering it highly visible at the national but also international level in infectious diseases.

The global level of science produced is excellent despite the heavy activity of NRC or plateforms that many teams are assuming and this has to be mentioned

Teams are very dynamic in different aspects of infectious diseases (epidemiology, immunology, microbiology, vaccinology, vector ecology, microbial pathogenesis...) working for most of them with a tranlational research view connected to real life.

Weaknesses and risks:

The connection between NRC and research activity is unequal and some teams benefiting from this opportunity should reinforce the use of the different types of materials issued from these activities.

It appears that teams in general can share more than a common global appartenance to a Department and that there are opportunities to share common approaches or methodologies to answer research particularities of each team. This has been started with sharing expertises of genotyping of pathogens, of establishing a very original aspect of analysing hispathology of animal models. This could be reinforced on epidemiology as well and thus generates a more translational research aspect based on expertises of the different teams.

There is heterogeneity of research emanating from these different teams which appeared not necessarily to fit with “host-pathogen interaction”

The intrinsic potential of research generated through the Department in well established teams should be better used to benefit more newly established teams.

There are some research activities which are of good qualities but which will be dismantled after retirement of team leaders.

Policies of hiring new teams on immunity and epidemiology in this department have been presented. However from the overall evaluation process, it appears that there is already a thread of very good scientists producing very good science whom it would be a pity to lose, and thus new resource may be better invested in supporting these teams than in recruiting new teams.

Recommendations:

Research identity of the department could be reinforced and there are strong possibilities which have not been fully exploited.

Possibly, the opportunity to give an independent budget to the department could reinforce cross collaborations and meetings between researchers in the Department.

3 • Detailed assessments

Assessment of scientific quality and production:

There is a high level of potential generating very good scientific quality and production but this is variable upon the different teams belonging to the department

Assessment of the unit's integration into its environment:

This department has a particularly high number of NRC/WHO activities which mostly, but not always, link to their basic research activities, thus connecting the research activities to Public health missions in infectious diseases, a long lasting tradition of Institute Pasteur

The constituting teams have been able to obtain external financing with very good efficacy, but the department has not been able itself to draw Labex financing, even though some teams are participating to such financing calls with other departments.

Assessment of the research unit's reputation and drawing power:

The strong connection of teams with NRC, WHO and the International network of IP is a very strong aspect of this department thus rendering it highly visible at the national but also international level; there are additionally teams with individual strong reputation and drawing powers.

Assessment of the unit's governance and life:

The governance of the department is a difficult task due principally to the heterogeneity of research aspects conducted; several axes have been successfully developed to push for sharing tools, models common to teams sharing basic research on infectious diseases. This has to be pursued to seal more teams under a research identity.

Members of the Department are involved in educational activities and there are 3 major courses fully assumed by members of the department, as well as training activities.

Assessment of the strategy and 5-year project:

3 main projects have been presented such as 1) reinforcing epidemiology and therefore highlighting this aspect as a task force; 2) hiring a junior group in the field of Innate Immunity, and 3) increasing the number of MD with full research training, the new epidemiology team project being classified as high priority and supported by Labex funding where the Department is partner. However, as mentioned above, there are some intrinsic ressources (human, scientific and methodological) that are surely unexploited and desserve particular attention.

Assessment of the unit's involvement in training:

There are strong and impressive training activities given and held by various teams.

From the audiences with the committee of the different personnel, several messages have been delivered:

-From the technicians, engineers and administrative support staff, it appears that some effort should be made in order to rationalize the work of the secretaries since one secretary is now assigned to different Units often distant in the campus, leading to inefficiency and frustration, and to recommend that Unit heads try to motivate technicians in their work by providing suifficient background on what they are doing and why. The last point seems to be unequally required in the different teams belonging to the Department.

-From the students and postdoctorate fellows audience, it appears that the PhD students are well organised and integrated within their environment. Several intiatives aimed at promoting scientific and social cross-fertilisation are arranged by a leading group of students, and no particular request or remark have emerged after the discussion with the visiting committee, apart from the willingness to receive part of their training in English language. Post-docs, especially those coming from non-French speaking countries have also express the same willingness. But their major concern is related to the duration of their contracts. In fact, 2 years of post doc research are not enough for allowing an appropriate scientific training and publication. The level of satisfaction among postdoctoral scientists and PhD students was remarkably high. All reported that they thought the Department was an ideal place to pursue their careers. Each student is supported by a senior scientist who monitors their progress and provides independent advice. The postdoctoral scientists appreciate the opportunities offered at the Pasteur Institute to initiate collaborations and to meet external visiting experts in the field. The department holds regular meetings for the students at which they present their research to each other. PhD/postdoc can take advantage of an intranet network where specific scientific questions can be posted,

allowing to find, within the network, the person/lab with the specific competence that will permit to tackle such question.

The postdoctoral scientists expressed concerns about their future career prospects given the limited opportunities in academia and industry, but there is little an Institute, let alone a single Department, can do about this except provide careers advice which they said they do.

-From the permanent researcher meeting, the general impression emanating from this audience was that many permanent researchers are questioning about their intra Pasteur Institute future, in particular with respect to several close team leader retirements and the lack of intra Institute perspectives due to highly competitive new team applications mainly offered to outside applicants.

4 • Team-by-team analysis

Team 1: Lyssavirus Dynamics and Host Adaptation

Team leader: Mr Hervé BOURHY

Workforce

Workforce	Number on 30/06/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors			
N2: EPST or EPIC researchers			
N3: Other professors and researchers	3 [1.1]	3 [1.8]	3
N4: Engineers, technicians and administrative staff * on a permanent position	6 [1.95]	6 [1.95]	
N5: Engineers, technicians and administrative staff * on a non-permanent position			
N6: Postdoctoral students having spent at least 12 months in the unit	2		
N7: Doctoral students	4		
N8: PhD defended	2		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar			
TOTAL N1 to N7	**15** [9.1]	**9** [3.75]	**3**

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:
http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

Team E1 has a very good level of scientific production (published papers and other means of scientific communication) in terms of quality (5 PLoS Negl Trop Dis, 2 Plos pathogens, 3 J Virol) and quantity (48). A major mission of the group that greatly determines its scientific strategies relates to the public health impact of rabies infections. The research has had a strong emphasis on phylogenetic procedures to define molecular epidemiological parameters in relation to disease emergence. The team has applied updated phylogeographical procedures to achieve its goals.

New, promising aspects of the research of this team initiated in the period 2007-2011, with plans to be continued in the coming 5 years, are structural studies, centred on the M protein in relation to host interactions and viral attenuation, and polymerase complexes. These structural studies, combined with biochemical and functional assays, should give rise new and more original investigations, as well as new avenues for drug design in the context of the SILVER project.

Research on host range modifications in combination with next generation sequencing (NGS) is planned and is expected to lead to new insights into the lyssavirus field.

Assessment of the research team's integration into its environment:

The team is fulfilling an important role in public health regarding rabies control. Probably because of dramatic social and environmental changes, some rabies infections are increasing in several world locations, and the activities of team E1 are a real need for public health. The group's activities are in the best tradition of the Pasteur Institute, they have managed to obtain external research funding, and they have joined a number of international teams and projects that should provide continuing financial and scientific support, and to improve research originality and impact. In particular the investigation into new viruses associated with encephalitis even of unknown origin is very relevant.

Assessment of the research team's reputation and drawing power:

The team leader has received two important awards and the group has trained a reasonable number of predoctoral and postdoctoral students, mainly from France, but some from abroad. The number of members that are permanent staff in the team seems to be rather limited in relation of the number and scope of the projects in which they participate. This is in part compensated by participation in many collaborations and programs with excellent scientists from France and other countries.

Assessment of the strategy and 5-year project:

The medium- and long-term scientific projects seem too broad to be able to be pursued in sufficient depth, despite each of them being supported by external, highly competent collaborations. The committee recommends that the unit focuses on some selected topics.

Biochemical and structural aspects of M oligomerization should be pursued, and it is expected that the participation of the team in the SILVER international network should open the possibility of new anti-lyssavirus targets for antiviral intervention. However, the studies on structure-function relationship and types of possible antiviral drugs (small molecules, peptidomimetics, etc.) are not described.

Conclusion:

The unit has performed well in the last five years and has the potential to perform even better in coming years. The unit offers an example of integration between a service/or platform and fundamental research.

Strengths and opportunities: They deal with very timely approaches and key research questions in virology. There is an excellent history of national and international contacts and productive collaborations. There are many possibilities to strengthen collaborations inside and outside the Pasteur Institute, and to engage in technological developments in the context of the superb facilities of Pasteur Institute.

Weaknesses and risks: The main weakness is that the broad program of activities proposed by the team will diminish the chances of in-depth research on any of the topics. Some general facilities at Pasteur, in particular informatics and bioinformatics supports (which are very important for this Unit and for other Units) seem to be limited at present.

Recommendations: The Unit is encouraged to sort out the most pressing needs from the point of view of public health, those from the point of view of basic research, identify points of interactions between these two activities, and propose a more focused work plan in line with the current interests of the Unit. As a general comment, the committee thinks that any platform or service should have fundamental research integrated in it. Absence of research activity has the risk of decreasing the quality of the routine, service work.

Team 2: Platform Genotyping of Pathogens and Public Health

Team leader: Mr Sylvain BRISSE and Ms Valérie CARO

Workforce

Workforce	Number on 30/06/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	0	0	0
N2: EPST or EPIC researchers	0	0	0
N3: Other professors and researchers	2	2	2
N4: Engineers, technicians and administrative staff * on a permanent position	4.8 [4]	4.8 [4]	
N5: Engineers, technicians and administrative staff * on a non-permanent position	0		
N6: Postdoctoral students having spent at least 12 months in the unit	2		
N7: Doctoral students	0		
N8: PhD defended	2		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	1	1	
TOTAL N1 to N7	**6.8** [6]	**6.8** [6]	**2**

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

The Platform Genotyping of Pathogens and Public Health can be characterized as a remarkable success in terms of contribution to technological innovation in bacterial genotyping and robust scientific production in the field of microbial genomics and genetics of human pathogens. Despite being a relatively young (6 year old) and small unit in terms of personel (8 members including two mid-career researchers and two post-docs in 2011) the unit has succeeded in establishing multidisciplinary expertise and build a fit for purpose, cutting edge technology platform fulfilling three concurrent missions: (1) high throughput genotyping support services to 20 other laboratories including Reference Centres for national and international surveillance networks; (2) active contribution to collaborative research projects with other Pasteur groups in the fields of pathogen discovery and rapid detection, genomics and molecular epidemiology of viral, bacterial and fungal pathogens as well as (3) developing its own original research program on diversity, emergence and phylodynamics of diverse bacterial pathogens of public health relevance.

The broad range and innovative capacity of its technical support are well documented in their detailed scientific activity report and publications and patents filed by the team. These data indicate development and validation of novel international molecular typing schemes (MLST, MLVA, CRISPR), development and maintenance of several open databases for multi-locus bacterial genotypes and development of whole viral genome sequencing and phylogenetic analysis strategies (Chikungunya virus, influenza virus A (H1N1)pdm09). Furthermore, the platform rapid reactivity in response to emerging threats was demonstrated by its collaborative genomic monitoring investigations of Chikungunya virus in the Indian Ocean and of influenza virus A (H1N1) during the 2009 pandemic wave in France. Results from a recent customer satisfaction survey and increasing demand by partner laboratories indicate recognition of quality and responsiveness of these services.

The group divides its list of 63 scientific publications in 2007-2011 according to its participation as service provider in collaborative projects (40 peer reviewed articles) and its own “Biodiversity and microbial populations” research program (23 peer reviewed articles and 2 book chapters). These papers were published in high ranking specialized journals in the field of microbial genomics, basic and medical bacteriology and virology and infectious diseases. The five most relevant publications by team members (with one of the co-directors of the platform as lead author for three of them) in the past five years were published in J Clin Microbiol, Emerg Infect Dis, J Virol, PLoS ONE and PLoS Pathog.

Through its “Biodiversity and microbial populations” research program, the group has provided key contributions to the understanding of global diversity and population structure, evolutionary mechanisms and pathovar emergence in important bacterial pathogens (Listeria monocytogenes, Klebsiella pneumoniae, E.coli, Salmonella and Acinetobacter baumannii. Their findings have led to a more unified picture of deep phylogenetic structure of known and newly delineated species within the large and ecologically diverse Enterobacteriaceae family. These advances benefit to development of novel molecular markers of significant interest for diagnostic, identification and epidemiological typing of these disease agents.

Assessment of the research team’s integration into its environment:

The group has established a solid network of collaborating laboratories both within and beyond Pasteur Institute, including with a large number French National Reference Centres and WHO Collaborating Centres supporting disease surveillance. Beyond providing technical genotyping services, it has actively contributed to improving the design and methods for enhanced genomic based surveillance of many pathogens of public health importance including food borne and healthcare associated pathogens. They have developed a strong collaboration with the unit E16 particularly on Shigella genome research. In spite of decreasing recurrent funding for its platform from intramural source and from the National agency (InVS), the team has maintained its funding level through participating in 11 collaborative grants from competitive intramural and external funding programmes. One industrial grant on diversity and in vivo genome stability of probiotic bacteria is held by a member of the team. In addition, two patents have been filed on the technological innovations made by the group leaders.

Assessment of the research team’s reputation and drawing power:

The group has established an extensive international network of collaborations with leading academic groups working on bacterial and viral genomics from the Netherlands, Germany, Czek Republic, Ireland, UK and the USA.

One of the co-directors of the unit has recently received two awards for outstanding scientific work (ESCMID Young Investigator Award and Deschiens Award of the French Academy of Medicine). He has also been awarded a Walton Programme Visitor Grant from the Science Foundation Ireland to develop an international collaborative project on

Salmonella population structure. He is the organiser of the next International Conference on Microbial Epidemiological Markers and has served on the executive committee of the ESCMID Study Group on Epidemiological Markers.

The team has attracted many students and post-docs comparatively to its size (11 for 7 staff members) and delivered two PhD theses.

Assessment of the strategy and 5-year project:

The strategic research plan for the next 5 years is well described, coherent and extremely promising both in terms of innovative services to the research and public health surveillance community but also in terms of original research in bacterial comparative genomics. The small "Biodiversity and microbial populations" is proposing an ambitious and original programme with several very promising projects aiming at elucidating by large scale population genomic analysis the emergence and phylodynamics of virulent bacterial clones. This programme is extremely important as it is likely to elucidate important questions on the evolution of major human bacterial pathogens. It benefits from a combination of strong competitive advantages: unique wealth of extensive historical collections of well characterised strains of global origin spanning a century of Pastorian reference work, linkage to detailed epidemiological metadata from surveillance programmes and close collaboration with leading molecular pathogenesis groups at the Pasteur Institute. The success of this programme will depend on sufficient capacity investment in latest generation equipment and stronger information technology support to data management.

The plan on viral pathogen discovery and detection is less well developed and focussed on demands from other units and the CIBU platform (E12).

Conclusion:

- The team is well integrated within the department and the Institute through its platform mission and cross-fertilisation between research and public health activities. It has successfully managed to provide excellent transversal genotyping service and at the same time ensure development of molecular epidemiology and surveillance approaches in the National Reference Centres that are based on robust bacterial population genetics framework.

- The team has initiated an excellent research programme on bacterial genomic diversity and evolution of several bacterial pathogens and has translated findings into new molecular typing schemes, bio-informatics tools and establishment of international genotype surveillance databases.

- The research projects on bacterial phylo-dynamics in collaboration with national reference centres and basic scientists across Pasteur departments appear likely to generate important insights on the emergence and epidemiological success of virulent clones. To enable the full potential of this promising programme, it appears timely to reassess allocation of time of this principal investigator between platform management and research as well as address capacity of bioinformatics and genomic data management support.

- The plan on viral pathogen discovery and detection appears sound and based on innovative methods but is less well developed and focussed on demands from other units and the CIBU platform.

Team 3: Cytokines and Inflammation

Team leader: Mr Jean Marc CAVAILLON

Workforce

Workforce	**Number** on 30/06/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors			
N2: EPST or EPIC researchers			
N3: Other professors and researchers	3	3	3
N4: Engineers, technicians and administrative staff * on a permanent position	1.45	1.75	
N5: Engineers, technicians and administrative staff * on a non-permanent position			
N6: Postdoctoral students having spent at least 12 months in the unit	4		
N7: Doctoral students	3		
N8: PhD defended	2		
N9: Number of Habilitations to Direct Research (HDR) defended			
N10: People habilitated to direct research or similar	3	3	
TOTAL N1 to N7	**11.45**	**4.75**	**3**

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

- Although good quality articles have been recently published, the level of publication (IF) could have been expected to be better/higher considering that the principal investigator is a world-renowned expert in the field of sepsis. This may be explained by the difficulty to publish translational research studies in high impact factor journals. Another explanation may lie in the relatively modest size of this research group (only 3 researchers and 1 permanent technician). This contrast is illustrated by the PI's H index (47). His papers are major references in the field and consequently are often cited.

- The number of PhD thesis / HDR obtained by students from the lab during the period of time between 2007 and 2011 is not provided.

- No patent recorded during the period

Assessment of the research team's integration into its environment:

- The leading researcher of the team is a member of many editorial boards, former president of international councils, organizers of several international congresses (e.g., euroconferences).

- The PI presents with an impressive list of courses given all over the world (Chile, Brazil, Mexico, Thailand, Lebanon, Uruguay, Romania….)

- During this period of time, he has been a member of jury of 9 PhD theses and 6 HDR.

- The team showed a good ability to obtain external fundings, participation to collaborative works (e.g., within PHRC or NIH programs).

- It has an important contract with industrial partners (i.e., bioMérieux, project CAPTAIN)

Assessment of the research team's reputation and drawing power:

- The team has an important presence in international congresses as invited speakers (and international courses)

- 1 researcher has been recruited in 2007,

- 7 post-doctoral fellows are listed over the period (average length of stay: 23 months)

- 3 PhD students defended their thesis over the period (average length of stay: 42 months)

- Many collaborations with foreign laboratories were developped over years, such as the one with a group in Boston (NIH grant) that gave a publication in JID in 2010.

Assessment of the strategy and 5-year project: good

This team presents a translational research program mainly focused on sepsis which remains a major public health concern all over the world (constant increasing incidence, severe mortality: stil 40 % for septic shock….). This program is well balanced between fundamental works and clinical/biomedical studies and includes several complementary aspects (diagnosis, pathophysiological mechanisms). Very few teams are conducting such work world-wide. However, regarding the size of the group there are probably too many ongoing projects.

Conclusion:

Overall opinion on the team: it has a very good publication record although not outstanding due to the difficulty of publishing such translational research. In sepsis and endotoxin tolerance, this group is within the top 3 world leading teams.

Strengths and opportunities: It is one of the best groups in the world in a field of translational research on sepsis, a research aspect that remains underdeveloped whereas it represents a key axis for the understanding of sepsis pathophysiology and development of novel therapeutics. The sepsis subject should be kept in the Pasteur Institute.

Weaknesses and risks: The small size of the group. The world-renowned reputation of the group is mainly based on the PI himself. This aspect has to be considered in the long-term evolution of the group.

Recommendations:

- The group working on fungal infections that joined the team in 2007 should be better connected with the overall projects. As an example, A. fumigatus infection is an emerging problem in ICU patients after sepsis. Some aspects (e.g., Th17) could be connected with ongoing biomedical research conducted with clinicians.

- Considering the difficulty to build large cohorts of patients in sepsis and related diseases, design of multicentric studies (even observational) should be considered.

- Due to too many projects, next research projects should be more focused.

Team 3 bis: TLR in *Leishmania major* infection

Team leader: Ms Noëlle DOYEN

Workforce	**Number** on 30/06/2011	**Number** on 01/01/2013	2013-2015 **Number of producers****
N1: Professors or assistant professors			
N2: EPST or EPIC researchers			
N3: Other professors and researchers	1	1	1
N4: Engineers, technicians and administrative staff * on a permanent position	1 [0.8]	1 [0.5]	
N5: Engineers, technicians and administrative staff * on a non-permanent position			
N6: Postdoctoral students having spent at least 12 months in the unit			
N7: Doctoral students	1 [from 2011]		
N8: PhD defended	1 [2008]		
N9: Number of Habilitations to Direct Research (HDR) defended			
N10: People habilitated to direct research or similar			
TOTAL N1 to N7	**3** [2.8]	**2** [1.5]	**1**

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

This small team focuses on the role of TLRs in the protozoal infection leishmaniasis. In particular, the team has been focusing on TLR9 and, to a lesser extent, TLR2, using mouse knockout models. The data are solid and have been published in appropriate journals. In general, however, the outputs over the relevant time period are low in terms of impact and quantity. This is likely a reflection of the team's small size and perhaps also the recent and future upheaval (retirement of previous PI, planned retirement of current PI). There is clearly a problem in terms of long-term planning and this has likely impacted on recent productivity.

Assessment of the research team's integration into its environment:

Leishmaniasis is an important and devastating disease and there is thus great socioeconomic value in improving our understanding of the etiological agent. However, the team has secured only two independent grants, which is on the low side but again likely reflects the short-term future of this team.

Assessment of the research team's reputation and drawing power:

The team has recruited postdoctoral researchers from foreign laboratories, but otherwise there is little evidence for significant international profile. This may largely be a result of the PI being 'projected' into this role after the retirement of the previous team leader.

Assessment of the strategy and 5-year project:

The team has a plan for the next four years (after which time the team leader plans to retire). There are some solid proposals (e.g. investigating the specificity of the DNA/TLR9 interaction) but the plan is somewhat unambitious and disorganised. In particular, no plans to extend their findings into human cells have been proposed, and there was little understanding of the significant potential of exploring the TLR9/DNA interaction. Strong recommendation is made for refocusing and potentially realigning this team.

Conclusion:

Overall this is a small team, whose outputs are solid but not internationally leading. They have clearly invested in establishing good murine based TLR models for leishmaniasis, which investment is a strength. However, the programme is somewhat unambitious and the failure to extend these findings into a relevant host cell type is a missed opportunity. Recommendation is made that some thought has to be given to the future of this team. Is it actually 'fit for purpose', given its small size and the likely retirement of the PI within the next few years, or would it be better subsumed into a larger research unit? If it remains independent, then some injection of new ideas (perhaps from new team members) will be essential.

Team 4: Innate Host Defence and Inflammation

Team leader: Mr Michel CHIGNARD

Workforce

Workforce	**Number** on 30/06/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	2	2	2
N2: EPST or EPIC researchers	2	1	1
N3: Other professors and researchers	2	2	2
N4: Engineers, technicians and administrative staff * on a permanent position	4 [3,1]	4	
N5: Engineers, technicians and administrative staff * on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	6		
N7: Doctoral students	5		
N8: PhD defended	5		
N9: Number of Habilitations to Direct Research (HDR) defended)	1		
N10: People habilitated to direct research or similar	4	3	
TOTAL N1 to N7	**22** [21.1]	**9**	**5**

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

- Although good quality articles have been recently published (J Immunol, Gastroenterology, Plos Pathogens), the number of papers and the level of publication (IF) could have been expected to be better/higher considering the amount of potential producers in the team (i.e., 4 researchers, an average of 4 post-docs + PhD per year) strengthened by 3 full time technicians,

- The H index of the team leader is 41 and other h indexes in the team are < 30,

- The team has good representation in international congresses as invited speakers,

Assessment of the research team's integration into its environment:

- Leading researchers of the team are members of different national and international councils (e.g. , the PI is president of the Gremi, president of the 10th world congress on inflammation) as well as organizers of several congresses (national and international),

- The team has good ability to obtain external funding, participation in collaborative works (e.g., within ANR program),

- A patent is recorded in 2010 (treatment of IBD),

- No contact with industrial partners is mentioned.

Assessment of the research team's reputation and drawing power:

- The team has a good presence in international congresses as invited speakers,

- 2 researchers have been recently recruited,

- 11 post-doctoral fellows were present over the period (average length of stay: 17 months),

- 6 PhD students were present over the period (average length of stay: 18 months),

- Several collaborations with foreign laboratories are mentioned.

Assessment of the strategy and 5-year project:

- This aspect is difficult to judge as two senior researchers (including the head of the lab) are going to leave the team, in particular the team leader. This fact is not taken into account in the feasibility of a medium- or long-term scientific project. Similarly, existence and relevance of a policy for allocation of means is not provided,

- Although the historical subject of the team was linked with P. aeruginosa / inflammation / lungs / acute pneumonia, it gave birth to many additional research subjects studying other germs (A.fumigatus, B. anthracis, Influenza A virus), other cells and pathophysiological mechanisms (epithelial cells, TLR, protease) and other pathologies (cystic fibrosis, COPD, IBD). Considering that 2 senior scientists are on the leave, the overall unit strategy should be better defined and focused,

- Moreover, as the group developed several models (cellular and animal) to assess pulmonary host response, a more translational orientation should be considered by sharing data and ideas with clinicians (or at least for discussion about strategy). As an illustrative example, the sole patent recorded during this period of time was related to the project studying the role of elafin in colitis which is not exactly the central interest declared by the team.

Conclusion:

Overall opinion on the team: This is a very well known group although not outstanding in a very competitive field (i.e., inflammation),

Strengths and opportunities: A good, almost excellent knowledge in pulmonary inflammation (including expertise in appropriate models, both cellular and animal),

Weaknesses and risks: too many ancillary projects, short-term leave of 2 senior researchers of the group (including the head of the lab),

Recommendations: Overall strategy should be redefined and focused considering the above mentioned weaknesses and risks. Considering the strengths of the group in basic pulmonary inflammation (without being outstanding), an alternative could lie in the development of a more translational research program based / focused on some unmet clinical needs especially since pulmonary disorders still remain a serious public health concern.

Team 5: Human Histopathology and Animal Models

Team leader: Mr Fabrice CHRÉTIEN

Workforce

Workforce	**Number** on 30/06/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	1	1,5	1
N2: EPST or EPIC researchers			
N3: Other professors and researchers	2	2	2
N4: Engineers, technicians and administrative staff * on a permanent position	4,8 [3,5]	4,8 [3,5]	
N5: Engineers, technicians and administrative staff * on a non-permanent position			
N6: Postdoctoral students having spent at least 12 months in the unit			
N7: Doctoral students	3,5		
N8: PhD defended	1		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	1	3	
TOTAL N1 to N7	**11,3** [10]	**8,3** [7]	3

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

This is a recently established dynamic unit which has rapidly integrated their activities with those at the Pasteur Institute. They provide support for several other groups within the Pasteur Institute and universities in the Paris area. The group makes original contributions in their respective fields through their expertise in both clinical and veterinary pathology. The quality of own research is of international standard and should be a valuable addition to the Institute. The laboratory also performs valuable service functions, which occupies about 2/3rds of their time. The unit tends to share joint authorships on publications as is typical for histopathology departments.

Assessment of the research team's integration into its environment:

Grant income has been good since the Unit was started, and includes support from other sources such as the ANR. Their work on 'tissue response to aggression and repair" is integrated well with several groups at the Pasteur Institute. This has led to extensive networks of research within the Pasteur Institute, which is impressive. The work on sepsis is highly interesting and original.

Assessment of the research team's reputation and drawing power:

There is no present evidence of their ability to win prizes and attract outstanding researchers, but this is a relatively young group and the effect of the Unit will be seen over the next few years. They have attracted 4 PhD students and 3 MSc students so this is an excellent starting point. Collaborations tend to be local rather than international which is in keeping with histopathological research. The expected move will provide an excellent opportunity to expand their work.

Assessment of the strategy and 5-year project:

The written report did not outline the research plans, but the presentation provided clear and original lines of research which should be encouraged; the work on stem cells/regeneration has particularly high potential. It would be helpful for them to outline novel technical developments, as this would be necessary to prevent the unit becoming only a service Unit.

Conclusion

Overall this is an excellent team. The strengths lie in their technical abilities and wish to address questions of fundamental importance. There is a risk that their ability to perform their own original research will be impaired by service commitments/collaborative projects. Their research time should be protected. They should consider developing novel techniques to advance the field.

Team 6: Molecular Mycology

Team leader: Ms Françoise DROMER

Workforce

Workforce	Number on 30/06/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	3 [1]	2 [0,5]	2
N2: EPST or EPIC researchers	1	0	0
N3: Other professors and researchers	1 [0,5]	1 [0,5]	1
N4: Engineers, technicians and administrative staff * on a permanent position	7.3 [3]	7.3 [3]	
N5: Engineers, technicians and administrative staff * on a non-permanent position	2 [1]		
N6: Postdoctoral students having spent at least 12 months in the unit	0		
N7: Doctoral students	3		
N8: PhD defended	1		
N9: Number of Habilitations to Direct Research (HDR) defended	4		
N10: People habilitated to direct research or similar	4	3	
TOTAL N1 to N(7	**17.3** [9.5]	**10.3** [4]	**3**

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

This team, in its current form, focuses primarily on the human fungal infection cryptococcosis. Over the period of consideration, they have been productive in terms of publications, and this covers a wide area within the field. A particular strength is their access to well-characterised clinical strains, which have been archived within the NRC centre. The team has exploited those to make a number of advances and resultant papers that are likely to have significant impact (e.g. mBio 2010). In general, there is a consistent, good to excellent quality, publication record considering the proportion of the team effort that is devoted to research (as opposed to NRC activity). Much of their recent efforts have been devoted to identifying in vitro correlates of clinical severity, which is an interesting and valuable idea although the committee would recommend some reorientation of the future directions to make better use of clinical material available to the team (see below).

Assessment of the research team's integration into its environment:

Fungal infections in general, and cryptococcosis in particular, are a growing clinical problem and there is therefore a strong socioeconomic necessity for this work. The amount of external funding for the team has been good, but has dipped recently. Given their ambitious plans for the coming years, the team should be encouraged to put more effort into securing more substantial, longer-term funding and capitalize on the unique resources they have available. In particular, the team has put effort into generating sets of well-characterised strains and possible clinical markers, both of which have significant potential for translational application and the committee would encourage the team to invest more in the validation of these approaches.

Assessment of the research team's reputation and drawing power:

The team leader is well-respected in the field of cryptococcosis but this has had limited impact in terms of international profile. There is good profile in terms of specialist/mycology meetings, but not broader, high-profile microbiology/infection meetings. Perhaps as a result of this, at present there are no international researchers in the team. A suggestion is made that a priority for the future would be to 'advertise' the team's strengths to the wider community in order to enhance their profile and international recruitment. Likewise, the number and breadth of international collaborations is not high, considering the resource (in terms of isolates, etc) available within the team. Strengthening this aspect will be critical for the future success of proposed research in rare fungal infections such as mucormycosis (see below).

Assessment of the strategy and 5-year project:

The future project plans are an interesting mixture of high-risk/high-gain projects and more routine (but still worthwhile) investigations. However, the diversity of future projects is potentially risky, in terms of spreading the team too thinly. There are number of areas that could be better addressed via collaboration, which would be a low-cost, high-speed way of achieving the aims of the project without requiring significant increase in resources or personnel. In particular, the proposed next-generation genome sequencing and associated RNA-seq lend themselves ideally to a collaborative approach with groups specialised in these technologies. Existing collaborators of the team (e.g. Broad Institute, Duke University, etc) already have this capacity and it could be recommended making the best use of these interactions to achieve these aims.

Several of the proposed projects have significant potential (e.g. the examination of dormancy in cryptococcosis and the detailed investigation of a potential 40kDa biomarker of clinical disease), but these are at an early stage. By focusing on these, very promising, avenues of investigation (rather than a wide range of areas) the team could potentially make major advances in the near future. In addition, some of the other proposed areas (e.g. biomarkers of filamentous versus yeast infection, examination of mucormycosis, etc) have potential but also the risk of diluting existing effort. These would be strengthened by having a large collaborative network, able to provide access to more strains, alternative technologies and additional clinical data that will be essential for the success of this approach.

Conclusion:

Overall opinion on the team: Very good – productive, diverse portfolio of interests, much potential for the future. However, the lack of international collaboration/profile is a major limitation, which may synergize with a very diverse future plan to heighten risk.

Strengths and opportunities: Strong publication record. Good set of diverse experimental tools (mouse models, cell models, antibody (and other) reagents, excellent access to clinical data and strains).

Weaknesses and risks: The team lacks international profile and team members, which is of particular concern given the high-risk (but very promising) future directions proposed.

Recommendations: There is no concern about the recent publication outputs. However, the future plan needs refocusing onto areas of strength and 'outsourcing' of certain approaches to collaborators in order to guarantee the success of the work proposed.

Team 7: Emerging Diseases Epidemiology

Team leader: Mr Arnaud FONTANET

Workforce

Workforce	Number on 30/06/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	0	1	1
N2: EPST or EPIC researchers	3	2	2
N3: Other professors and researchers	3	2	2
N4: Engineers, technicians and administrative staff * on a permanent position	5 [2.5]	5 [2.5]	
N5: Engineers, technicians and administrative staff * on a non-permanent position			
N6: Postdoctoral students having spent at least 12 months in the unit	2		
N7: Doctoral students	3		
N8: PhD defended	4		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	2	2 + 3?	
TOTAL N1 to N7	16 [13.5]	10 [7.5]	5

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

According to its double mandate, the E7 Emerging Diseases Epidemiology research unit has divided its activities over the past decade between an original research programme on the epidemiology and management of hepatitis C in Egypt and epidemiologic and biostatistical support to other research programmes within the International Network of Pasteur Institute, including studies of HIV infection, meningo-encephalitis, influenza and Buruli ulcer.

The scientific report and listed publications of the team attest that this research group has significantly contributed to a clearer appraisal of the public health impact of the world largest and ongoing epidemic of hepatitis C in Egypt and led to a better understanding of the iatrogenic risk factors associated with local transmission. Their research findings have demonstrated the efficacy of standard combination therapy with pegylated interferon α-2a- ribavirin in patients chronically infected with the locally prevalent viral genotype 4. In addition, scientists from the team have contributed their expertise to clinical epidemiologic and aetiologic studies led by other international research groups on management of HIV-infected patients in countries with limited resources in Africa and Asia.

The research unit presents a solid publication record with 112 peer-reviewed papers published in leading international journals over the five year period 2007-2011.Of 100 original research articles, approximately 25 were published in journals with Impact Factor (IF) >5 and 9 in journals with IF >10. The five most relevant publications with team members as lead authors were published in top ranking journals with IF range from of 6.4 (AIDS) to 33.6 (Lancet). Given the number of researchers (6) and post-doctoral scientists (2), this amounts to approximately 2.5 publications per scientist annually. In addition, team members have authored three book chapters and edited two books. Overall, the publication output of the group appears adequate in quantity and excellent in quality, given the size of the unit and the substantial workload dedicated by senior team members to teaching and service activities.

Assessment of the research team's integration into its environment:

The group has established strong working relationship with health researchers and policy makers in Egypt thereby, allowing a major societal impact of their work in terms of capacity building of scientific infrastructure and advising public health policies. The team leader is member of advisory committees for the Egyptian Ministry of Health and an influential contributor to the national hepatitis prevention and treatment strategies. The collaborative programme established with Egyptian partners is truly remarkable. The relevance of research questions and successful translation achieved between rigorous scientific investigations and design of intervention strategies is a model for evidence-based public health. The very fact of the continuity of work with partners amid political turmoil bespeaks of the quality and added value of these contractual relations.

A list of 26 research grants obtained in the period 2007-2011 (section 5) indicates extensive extra-mural funding from competitive applications to a range of national, European and international agencies. Of note, only three of the six researchers are mentioned as grant holders. For the majority of these grants, the amount going to the unit is below 100 000 euro as the major part of the funding is supporting capacity building, organization and management of studies at field sites in Asia and Africa.

The contribution of the group to advanced education and training as part of its partnership with foreign universities and Pasteur Institute abroad and in the framework of an original Master Course in a newly created School of Public Health is to be commended as extremely valuable in building capabilities in the global public health community.

Assessment of the research team's reputation and drawing power:

The senior researchers of the team are recognized experts of international standing in their field as indicated by their participation to national and international scientific advisory committees in health research and public health fields, membership of editorial board of scientific journals of high standing, and invited professorship or lecturer at top-ranking national and foreign higher education institutions.

The team has been successful in attracting highly qualified researchers, doctoral students and post-docs, presumably from France. It is gathering a well-balanced multidisciplinary team with a strong combination of expertise including social sciences such as anthropology and demography that are well suited to its blend of epidemiological, biomedical and public health research and training activities.

The group is excellently placed in terms of effective collaborations in a large number of projects in study sites across the international network of Pasteur Institute in Africa and Asia. It has also developed a very promising collaboration with advanced biomedical research groups in human genetics, immunology and virology to conduct cross-disciplinary study of biological markers of HCV spontaneous clearance based on the constitution of extensive biobanks linked to large and well documented clinical cohorts of acutely infected HCV patients.

Assessment of the strategy and 5-year project:

The future directions and next five year project of the team are shortly presented and mostly focused on HCV studies with less information on other research topics. The HCV research objectives are relevant and well described. Building on previous achievements on the identification of HCV transmission patterns, the main areas of continued hepatitis C research in Egypt are logically addressing (1) the efficacy and safety of novel drugs, drug combinations or drug formulations in clinical trials, (2) cultural and behavioural determinants of unsafe injections and invasive medical procedures to design prevention interventions (3) effectiveness and cost-effectiveness analyses by mathematical modelling and community intervention trials and (4)"omic"- based analysis of biomarkers in observational cohort studies in search of viro-immunological and genetic determinants of HCV clearance during acute infection.

These projects are highly relevant, scientifically robust and likely to generate important new information on hepatitis C disease determinants and innovative prevention and treatment options. The proposed methodology is well designed and ideally suited to the expertise of the group and their unique collaborative arrangements with clinical and community research teams in the field. Moreover the foreseen studies appear to be adequately supported by available grants and collaboration with pharmaceutical companies.

The description of planned activities and research approaches on other diseases is ambitious. The report cites several projects to be conducted in collaboration with the international network of Pasteur Institute in Africa and Asia, including on the epidemiology of Buruli ulcer and the aetiology of acute diarrhea and encephalitis. No further work in the area of HIV infection is mentioned even though this has been a productive area of the group. Although the research questions for the planned studies appear sound and the study design appropriate, their strategic coherence is not apparent. The specific contribution of the team and its strategy in the participation in epidemiologic investigations of other diseases than hepatitis C builds on its experience and methodological expertise.

Conclusion:

The team has built a strong multidisciplinary expertise portfolio. They are scientifically very productive with a sustained stream of national and European funding, excellent publication record and achieved international recognition for its seminal contribution to the epidemiology of HCV infection.

- Its programme of future hepatitis C research appears very promising and competitive and should ideally lead to breakthrough publications in top ranking medical journals.

- Beyond HCV research, the team plans for methodological support to cross-disciplinary studies by Pasteur affiliated groups on transmission of M.ulcerans, aetiology of paediatric diarrhoea and encephalitis are very interesting and well supported by partnership with competent field investigators and secured funding for the coming years.

- The contribution of the group to education and training programmes in public health and infectious diseases epidemiology grounded in research is remarkable and certainly worth supporting. It could benefit from further international collaborations.

- The collaborative programme developed in Egypt is a model for international public health research and capacity building. Likewise, the effective translation of epidemiological research findings of the group into public health policy is outstanding and should be strongly supported.

Team 8: Antiviral Immunity, Biotherapy and Vaccine Unit

Team leader: Ms Marie Lise GOUGEON

Workforce

Workforce	**Number** on 30/06/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	0	0	0
N2: EPST or EPIC researchers	0	0	0
N3: Other professors and researchers	1	1	1
N4: Engineers, technicians and administrative staff * on a permanent position	3.3	3.3	
N5: Engineers, technicians and administrative staff * on a non-permanent position			
N6: Postdoctoral students having spent at least 12 months in the unit	3		
N7: Doctoral students	2		
N8: PhD defended	2		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	1	1	
TOTAL N1 to N7	**9.3**	**4.3**	**1**

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production

This is a relatively small unit well organized in two parts: one is dedicated to research; the other one is a platform supporting biological investigations in the field of immunity and vaccine development. The organization of the lab theoretically offers the ability to improve knowledge acquired in the research department for investigations and clinical studies. The group has also several collaborations, either with basic research groups, or in the field of applied research in vaccine development. The total funding since 2004 is approximately 1.5 Meuros, most of these grants as principal investigator and a significant part is related to the immunomonitoring platform.

At the scientific level the group is specialized in NK and DC cells and their respective roles in HIV pathogenesis and control. In a step by step approach the group has conducted a series of investigations describing the impact of HIV on the maturation and function of DC cells. They have been able to discover some mechanisms that modulate the fate of DC cells and could be relevant in transmission of HIV to CD4 cells. Their experiments suggest that cross talks between NK cells and DC cells play key roles in early steps of HIV infection in humans. They have identified that a HMGB1 was responsible for HIV persistence in DC cells by preventing killing by NK cells (DC escape from TRAIL-dependent NK-mediated killing).

Recently the team has participated to a study looking for marker of HIV central nervous system related complications. This was an opportunity to assess whether their in vitro findings could be relevant in HIV infected individual. This preliminary investigation was possible thanks to the combination of their basic research results and the large screening of different inflammatory markers in cerebrospinal fluid of HIV infected patients using the immunomonitoring platform. This has lead to identify HMBG1 as a possible marker of disease.

For the research group the immunologic platform offers theoritically opportunities that could promote translational medicine. Although this platform provides specialized tests for investigators and cannot be considered as a research group per se, it is a very important tool and opportunity for clinical investigators that do not have a specialized laboratory available and the team has largely used the platform for collaborative research projects.

The size of the group is relatively small, and the group could benefits from additional PhD or investigators. In term of external funding, the number of grants that have been collected, either by the principle investigator, or in collaboration with other groups is very significant. It is not clear whether there is a policy to promote young promising investigators or to attract researchers in the group. The staff of the research group is limited and made mainly of PhD or students. This being said, the group has attracted PhD students and post-Docs.

In term of publications, the number of publications during the last few years is quite high considering the size of the unit but many or most of these publications result of collaboration with other groups thanks in part to the immunomonitoring platform. Some of these publications are in high impact journals and several basic research publications are also highly visible. Nevertheless, the number of original publications of the research group itself (first and senior authors of the E8 team only) could be higher.

Assessment of the research team's integration into its environment

The integration in the Institute is excellent, the main reason being the immunomonitoring platform. The team participates in many different types of studies and vaccine development despite the lack of specific expertise but provide technical tools for investigators. This is both an advantage but also a potential weakness since the research group cannot provide complete scientific expertise for most of these activities and some projects are limited to one investigation. The level of interactions between the two parts of the unit is thus potentially limited. Nevertheless thanks to these collaboration and co-authorship the group found the motivation to run the platform. The level of international collaborations is good with several significant European collaborations.

Assessment of the research team's reputation and drawing power

The scientific production of the team is relevant and of excellent quality, the number of publications given its size is quite impressive. Although the group has co-authored recently many excellent publications, very high profile publications from the group itself are lacking. The number of presentations at international meetings is good but could be higher, a higher visibility might be expected at the international level in the field of HIV.

It seems that attracting more post-doctoral fellows might be possible and feasible given the activities of the group, but it is not clear whether this group wants to keep a small size.

The immunology platform is certainly an interesting activity that provided important opportunities for projects conducted by other groups not only at Pasteur Institute but also by other French groups. Although this platform offers an important expertise and co-funding, the real added value for the research group is difficult to assess. Many of these projects are dealing with immunology but in very different fields ranging from auto-immune diseases to bacterial vaccines and immune interventions. Most of these projects are not directly related to the main research field. Still this platform has proven to be necessary and the number of projects that have used it is important.

Assessment of the strategy and 5-year project

The committee recommends to keep a strong focus on the role of NK and DC cells in control of viral diseases. Otherwise there is a risk to dilute the expertise of the group particularly given the type of collaborations generated by the immunomonitoring platform. Consider to increase the size and the resources directed toward the research group also by promoting synergies thanks to close collaborations with other units working in the field of HIV and immunity. At the research level the role of NK and DC cells in HIV pathogenesis is a strong field of investigations for many years and also in future projects. The future plan for additional experiments is well organized and clear. This is certainly strength to the E8 team. It seems however that this activity is mainly dependant on the principle investigator and at this point there are no other researchers within the team that could develop complementary activities.

The basic research activity has also led to a few translational projects that were conducted by the immunomonitoring group, this type of translational projects should be encouraged and promoted but should not weaken basic research activities.

Immunomonitoring activity: there is a very large diversity of investigations in different fields. The goal is to provide a platform for all kind of investigations (bacterial, viral…) and to provide the most adapted immunological investigations: The opportunities and work done by this platform is interesting and even impressive: the adaptability of this platform needs to be conserved. However the committee takes note that in most of these projects the research team is not the leading party.

Conclusion:

The ratio between the overall scientific production and the size of the team is considered excellent. The recommendation is that the group keeps a strong focus on basic research on the role of NK and DC cells in control of viral diseases. Otherwise there is a risk to dilute the expertise of the group particularly given the type of collaborations generated by the immunomonitoring platform. Consider to increase the size and the resources directed toward the research group also by promoting synergies thanks to close collaborations with other units working in the field of HIV and immunity.

Immunomonitoring activity: there is a very large diversity of investigations in different fields and this type of expertise is needed within the Pasteur Institute. The group has seized the opportunities provided by this platform and this should be noticed.

Team 9: Pharmacoepidemiology and Infectious Diseases

Team leader: Mr Didier GUILLEMOT

Workforce

Workforce	Number on 30/06/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	1 [0.5]	5 [1.6]	1 [0.5]
N2: EPST or EPIC researchers	2 [1.75]	3	2 [1.75]
N3: Other professors and researchers	0	1	0
N4: Engineers, technicians and administrative staff * on a permanent position	2	1	
N5: Engineers, technicians and administrative staff * on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	0	1	
N7: Doctoral students	3		
N8: PhD defended	2		
N9: Number of Habilitations to Direct Research (HDR) defended	2		
N10: People habilitated to direct research or similar			
TOTAL N1 to N7	**9** [8.25]	**11** [6.6]	**3** [2.25]

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

The team has built on a strong and coherent collaboration between epidemiologists, statisticians and mathematicians, to try understanding and modeling how the implementation of anti-infective interventions (antibiotics or vaccines) affects microbial escape strategies. This multi-parameter and complex dynamics is addressed at several levels, recently including social sciences. Ultimately, the research seeks to understand the complex and constantly evolving host-microbe interaction, at the level of selection of drug resistance or the interaction between the host and more than one external factors, including viral infection, bacterial pathogens, vaccines, antibiotics, drug pharmacokinetics and population compliance. The ongoing research uses model systems utilizing large programs targeting antibiotic over-usage and anti-pneumococcal vaccines in France and elsewhere. These programs are resulting in much more complicated effects than anticipated. For instance, the group showed that while decreasing antibiotic consumption decreased the prevalence of antibiotic resistance, the simultaneous utilization of 7-valent anti-pneumococcal vaccine promoted an increase in pneumococcal meningitis due to new serotypes not covered by the vaccine, but susceptible to antibiotics. Interestingly, these episodes were classically following viral superior respiratory infections for with antibiotics were often (falsely) given in previous medical practice. Hence, since these meningitis bacteria were due to drug-susceptible strains, they might have been paradoxically prevented by former habits. This restores the usefulness of antibiotics, provided that they are adequately applied. Moreover, it raises awareness against simplistic thoughts that vaccination will solve all infectious diseases issues.

Such provocative questioning is important for society. It is further prolonged in the program of vaccination against HPV, which includes its intrinsic risks such as viral antigenic variation and public hostility. Together, these two examples represent remarkable paradigms of continuing issues in applying public health measures.

The research irradiates in several other domains via collaborations with university hospitals, which help address additional issues, such as methicillin-resistant Staphylococcus aureus (MRSA). At this stage the publication track of original contributions is rather good (from 32 original publications plus 11 with collaborations), but the number of publications with affiliate hospitals is close to 200, thus highlighting the dynamic of external collaborations.

Assessment of the research team's integration into its environment

The research of the team is well integrated in its epidemiological environment, as shown by multiple collaborations and supports by large national and European cohort projects (e.g. DyPAVIr-ISHARE for HPV, 1,500 KEuros, ChARLI for drug resistance in children from low income areas, 700 KEuros; IBIRD for individual based investigation of resistance dissemination, 450 KEuro) to a total of close to 3,000 KEuros shared with partner groups. These projects are part of a global effort to model and prevent microbial escape to anti-infective interventions. The modeling project has generated an original software (Nososim) helping prediction of nosocomial pathogen dissemination.

Assessment of the research team's reputation and drawing power:

The group has certainly attracted international recognition via two seminal publications in PloS Med and PNAS on antibiotic surveillance and in silico modeling of dissemination of antibiotic resistant strains. It has also attracted promising young staff members in statistics and bio-mathematics, who are developing novel algorithms to simulate the dissemination of multi-resistant pathogens. Staff also includes five post-docs and PhD students. In this context, attracting young scientists in mathematical modeling of biology should be even more encouraged.

Assessment of the strategy and 5-year project:

The proposed program matches factual acquisition and interpretation of epidemiological data with new developments in mathematical modeling of bacterial colonization, dissemination and disease. Factual data will be retrieved from ongoing large cohorts such as the IRBID and ChARLI programs, which follow thousands of patients or volunteers for microbial colonization and infection, and collect numerous data on parameters including microbial phenotypes, patient's characteristics and environmental issues. For instance, the IRBID swabbing program already collected >10,000 samples, including ca. 3,000 S. aureus isolates. These large databases are pertinent for the program feasibility, which aims at characterizing ecological factors important for successful strain dissemination.

In parallel, these data will feed the development of new mathematical modeling techniques, run by the team of statisticians and bio-mathematicians. The aim is to achieve mathematical models accurate enough to predict the possible outcomes of novel types of interventions, such as, for instance, those resulting from simultaneously decreasing antibiotic utilization and implementing new vaccines against pneumococci. While this summarizes the basic concept of developing models to appraise the evolution of the host-microbe relationship following a new type of anti-infective intervention, the

topics are potentially multiple. The team envisions studying primarily MRSA and extended-spectrum beta-lactamase producing enterobacteria. However, it also plans to extend modeling to follow and predict the evolution of HPV after the introduction of large-scale vaccination, which is a genuine public health issue in the next few decades.

The project is sound but challenging. One may object that simulating complex epidemiological systems is to complicate to be successful. On the other hand, it is the very issue challenged by systems biology. Not tackling that type of development would be a mistake.

Conclusion

- The team is relatively young (created at Pasteur in 2008) and has yet not achieved an expected outstanding scientific reputation. On the other hand, it has attracted the interest of multiple large-scale national and European programs, essentially for its dissemination modeling initiative. The proposed program is ambitious and challenging.

- The positive points are the new emerging domain of modeling in epidemiology, the access to large databases, and the enthusiasm of young researchers in computational sciences.

- The challenges are the symmetry of the positive points. The research should aim at appropriate validation of the mathematical models, in order to be useful to predict potential outcomes of new interventions, i.e. identify potential weaknesses or problems in order to prevent them.

- Modeling complex systems is potentially very promising but challenging. Developing such expertise in this team will require the development of strong database management, and strong IT and mathematician support.

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Team 10: Molecular Prevention and Therapy of Human Diseases

Team leader: Ms Nicole GUISO

Workforce

Workforce	**Number** on 30/06/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors			
N2: EPST or EPIC researchers	1	1	1
N3: Other professors and researchers	1	1	1
N4: Engineers, technicians and administrative staff * on a permanent position	En 3 [1.5] Tech 2 [1] Adm 2 [1]	En 3 [1.5] Tech 2 [1] Adm 2 [1]	
N5: Engineers, technicians and administrative staff * on a non-permanent position	2 [1.8]		
N6: Postdoctoral students having spent at least 12 months in the unit	3		
N7: Doctoral students	4		
N8: PhD defended	1		
N9: Number of Habilitations to Direct Research (HDR) defended	2		
N10: People habilitated to direct research or similar	2	2	
TOTAL N1 to N7	**18** [14.3]	**9** [5.5]	**2**

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

The laboratory hosts two NCR (for Bordetella spp. and Corynebacterium spp.) and is composed of three research groups. Groups 1 and 2 are working on Bordetella spp. and Corynebacterium spp., respectively. Group 3 works on structural biology and protein-protein interaction with Dengue antigens.

Group 1: Works on Bordetella spp., a research that has been going on since many years. It is focusing on strain evolution under the selective pressure of large-scale vaccination. The observation is that whole-cell Pertussis (Pw) vaccine, available since many years, has eliminated the vaccine strains (as determined by PFGE typing) from the population, but that these strains have been replaced by others. Moreover, when Pw vaccine was replaced by acellular Pertussis (Pa) vaccine (directed against specific bacterial virulence factors) in the late 1990, Pa vaccine was followed by another shift in colonizing Pertussis PFGE-types, implicating strains which lost vaccine target genes or expression of their determinants, thus resulting in genome simplification. Nevertheless, while these simplified strains should be less virulent, they are still able to colonize and maybe to develop new invasive strategies. Indeed, clinical evidences indicate that new types of Bordetella spp. are arising in certain patients, including infection due to animal and environmental B. pertussis precursors B. bronchiseptica and B. petrii. Research on this fascinating evolution is associated to the development of PCR-based diagnostic tools, which is part of an important contribution to public health activities.

Group 2: Works on Corynebacterium spp., a research line that has been launched only since 2009, following a regain of imported cases of tox+ diphtheria and the parallel discovery of autochthonous cutaneous and respiratory cases due to tox+ C. ulcerans. This renewed interest in Corynebacterium spp. has led to retyping these organisms with new techniques (e.g. MLST) as well as to discover invasive cases of tox- C. diphtheria. Although the size of this group is limited, it is responsible for a NCR and for providing new diagnostic tools.

Group 3: Research implies structural biology and engineering synthetic epitopes of Dengue viruses to help the detection of serum antibodies and produce specific molecular tools for accurate diagnosis. In this line, the group is also active in developing reagent-less biosensors that could signal directly the presence of antibodies without requiring double-layer ELISA-type of assays. Eventually, the group is also active in studying the structure-activity relation of ribosomal protein SA, a multifunctional polypeptide acting as cell surface receptor for Flaviviruses.

The three groups are publishing at good to very good level both individually and together. However, there is an evident hiatus between their specific interests. They shared a common interest in developing therapeutic anti-Bordetella antibodies few years ago, but this program has become a low priority on the agenda.

Assessment of the research team's integration into its environment:

Groups 1 and 2 are responsible for two NCR for Bordetella spp. and Corynebacterium spp., respectively. The epidemiological importance and workload of such activity is substantial. Group 3 is active in technological transfer and holds at least three recent (since 2008) patent applications in the name of the Pasteur Institute and the CNRS. Besides, the three groups have continuously and successfully raised external funds from national and European projects as well as from industrial partnerships over the period under review.

Assessment of the research team's reputation and drawing power:

The groups have a good national and international visibility altogether. Besides the two NCR, the Bordetella group is also expert member in its domains at the WHO. Likewise, the PI of group 3 is advisor of the IFP-Energies nouvelles and member of the editorial board of the journal "Protein engineering, design and selection" (Oxford University Press).

Assessment of the strategy and 5-year project:

Groups 1 and 2 plan to continue their current research activities. First on the epidemiology of Bordetella spp., the impact of the Pa vaccine on such species, the duration of vaccine coverage (plus the development of vaccines for animals), and the development RT-PCR-based diagnostic tools. Second, on the spatio-temporal analysis of tox+ and tox- Corynebacterium spp. in France and other countries, typing by MLST, determination of tox expression, RT-PCR detection tests, and evolution of antibiotic resistance.

The program is based on solid ground and thus feasible. However, the committee finds it frustrating not to find more prospective questions addressing for instance the ecology of these organisms at a more general scale. Potential questions include: what are the species and population genetics in healthy carriers, are these populations affected by large-scale vaccination as well, do these organisms come in addition to the normal ENT flora, can peculiar oropharyngeal

microbiome protect from colonization, what is the implication of the host's genetic etc. Moreover, since new emerging strains have lost some pathogenic factors but have regained virulent, research on such new virulence mechanisms should be planed. Such questions would add knowledge on the normal ecology of these organisms in non-diseased people, an aspect that is often overlooked in appraising the global picture of microbial colonization.

Group 3 plans to address unanswered questions of its current developments in protein-protein interaction and structure-activity relations. While this is sound as well, it would be interesting to have some plan for validating and implementing these tools in the field.

Conclusions

- Individually, groups 1-2 and 3 are focused and performing well. However, in both cases (and considering the broad knowledge of groups in their respective domains) the 5-year project would gain from more ambition in questioning either novel dimensions of the normal microbe ecology or pathogenicity (groups 1-2) or jumping to field validation and implementation (group 3).

- Groups 1-2 have access to the long-term medical history of vaccination and host-pathogen evolution. It would be on tremendous interest to draw a global (e.g. metagenomic) picture and virulence evolution of such peculiar biomedical evolution. Group 3 has a very high-tech grasp on key aspects of nasty and public health concern Dengue fever. It should seek collaboration with groups interested in this scourge.

- Groups 1-2 and group 3 are living different lives on common resources. They should consider reorienting partnerships.

Team 11: Microbes and host barriers

Team leader: Mr Marc LECUIT

Workforce

Workforce	Number on 30/06/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	1 [0.8]	1 [0.8]	1 [0.8]
N2: EPST or EPIC researchers	1	2	1
N3: Other professors and researchers	2 [1.2]	2 [1.5]	2 [1.5]
N4: Engineers, technicians and administrative staff * on a permanent position	5 [2.5]	5 [2.5]	
N5: Engineers, technicians and administrative staff * on a non-permanent position	0		
N6: Postdoctoral students having spent at least 12 months in the unit	4		
N7: Doctoral students	4		
N8: PhD defended	2		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	2	3	
TOTAL N1 to N7	**17** [13.5]	**10** [6.8]	**4** [3.3]

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

The PI of the team is a full professor in infectious diseases, at Paris Descartes University's Medical School. He has clinical duties at the hospital Necker-Enfants malades. He was awarded a very competitive Inserm-avenir group, and since 2008, is leading a 5 year group at the Pasteur institute. He is interested in understanding the molecular mechanisms underlying the ability of microbes to target specifically cells and tissues, disseminate into the host and cross the intestinal, blood-brain and placental barriers. He is interested using in vivo approaches in two model bacterial microorganisms: Listeria monocytogenes and Group B streptococci, and very recently he initiated another research program around Chikungunya virus, which has also a neurotropism.

It is a small unit made of Dr Lecuit and two senior staff scientists (a Pasteur senior scientist and a recently recruited INSERM CR2), one technician, and non-permament staff (post-docs, PhD, master students).

The productivity of this team is outstanding (2 Nature, 3 J Exp Med, Two Plos pathogens, Plos Medecine, Cell Host Microbe, Nature Protocols, and Nature review Microbiol) and at the highest level of groups at the Pasteur Institute. The PI is a recognised world-leader in listeriosis and microbial pathogenesis, both highly competitive fields. The rapid response to the Chikungunya (CHIKV) epidemic was particularly impressive, and demonstrates that the group can initiate novel projects in line with current and emerging health threats.

Assessment of the research team's integration into its environment:

The group is well integrated at Pasteur Institute, and collaborates with other units within the Pasteur extensively. The grant income has been particularly impressive, especially including the ERC European starting investigator award. . The team is in an excellent position to benefit from running the NRC in listeria, as this might provide information about host susceptibility and microbial pathogenesis.

Assessment of the research team's reputation and drawing power:

The head of the group has a high scientific profile and is a potential future research leader in microbial pathogenesis. He is integrating the work of the team with the NRC for listeriosis to which they are attached. He has been awarded multiple national and international prizes. The team has already recruited an INSERM funded researcher, which is evidence of the attractiveness of the group. Furthermore, it was able to attract 4 post-docs (2 more to come), 4 phD students and 2 Master students.

Assessment of the strategy and 5-year project:

This is a balanced ambitious programme of research with the group taking basic molecular aspects of pathogenesis and integrating it with current important clinical problems with available clinical and strain databases. It is expected that the research programme will yield results of not only fundamental scientific importance but also with benefits by being translated into human health. A particular strength of the group is their emphasis to study pathogens from bench to bedside, which is derived from the group leader's clinical training.

Conclusion:

Overall, the commitee was impressed by the outstanding production of this group. It is a young and dynamic team. The strengths are evident from the scientific output, importance of the research questions and from performing detailed work on pathogens in vivo through ground-breaking technology.

Given the quality of the results, the very competitive field of microbial pathogenesis, and the focused hot topics investigated, the committee felt that this group would benefit from expansion (work space and man power).

Team 12: Urgent Response to Biological Threats (CIBU)

Team leader: Mr Jean Claude MANUGUERRA

Workforce

Workforce	**Number** on 30/06/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	1 [0.5]	1 [0.5]	1
N2: EPST or EPIC researchers	0	0	0
N3: Other professors and researchers	3 [0.7]	2 [1]	2
N4: Engineers, technicians and administrative staff * on a permanent position	10 [2]	8 [1.6]	
N5: Engineers, technicians and administrative staff * on a non-permanent position	1 [0.5]		
N6: Postdoctoral students having spent at least 12 months in the unit	2 [2]		
N7: Doctoral students	1 [1]		
N8: PhD defended	2		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	4	3	
TOTAL N1 to N7	**18** [6.7]	**11** [3.1]	**3**

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

This team has a very good publication record, as well as an excellent performance as a unit to respond to disease emergences (an aspect which has not been the focus of the present evaluation). The group has also participated in scientific books, and many national and international conferences.

Assessment of the research team's integration into its environment:

The team has two very well focused projects: 1) the identification of pathogens (both viral and bacterial) and 2) survival of viruses outside their hosts. They have responded adequately to unexpected threats such as the advent of the influenza A H1N1 2009 pandemic, or the increasing possibility of avian influenza viruses to become human pathogens, among other activities. They have demonstrated a good capacity to obtain research grants.

Assessment of the research team's reputation and drawing power:

The team members have participated in an impressive number of national and international scientific meetings. The number of permanent scientists (4) appears to be very small relative to the research potential of some of the team activities and findings (discussed in more detail below). A reasonable number of temporary scientists (trainees, pre- and post-doctoral students) are listed, as well as many engineers, technicians, administrative and laboratory staff. Incorporation of a new scientist to reinforce research activity is recommended.

Assessment of the strategy and 5-year project:

The scientific projects are well focused, and they are clearly feasible. As presented, they guarantee both continuity and progress. They combine development of new methodology (for example, whole genome amplification procedures, multiplex microarray applications, etc.) with diagnostic validations, and developments that are in the forefront of scientific research (for example, the discovery of new viruses such as a human Gyrovirus, a new human polyomavirus, and the new neurovirulent strain of TMEV termed NIHE). Nevertheless the committee has the impression that an adequate choice of collaborations to further characterize the new viruses genetically, functionally and structurally could have enhanced the impact of these findings.

The prospect of expanding research towards high throughput sequencing seems very adequate in view of our current understanding of diversity in the microbial world. In particular, pursuing third generation single molecule real-time sequencing (Pacbio, pacificbiosciences.com) is strongly encouraged.

Conclusion:

The team describes a SWOT analysis that should serve as the basis for reconsideration of some team strategies. Perhaps it can be added with regard to the opportunity offered by the new building related to disease emergence, that an increase in scientific staff, and the finding of active collaborators in virology may provide an opportunity to characterize new viruses and increase the impact of the group in terms of publication and public perception. Finally, an added strength is that restricting the activities of the team to Themes 1 and 2 provides a focused aim that renders the proposal for future work highly realistic.

Team 13: Insects and infectious diseases

Team leader: Mr Paul REITER

Workforce

Workforce	**Number** on 30/06/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	1	1	
N2: EPST or EPIC researchers			
N3: Other professors and researchers	0	2	1
N4: Engineers, technicians and administrative staff * on a permanent position	1		
N5: Engineers, technicians and administrative staff * on a non-permanent position			
N6: Postdoctoral students having spent at least 12 months in the unit	1		
N7: Doctoral students	1		
N8: PhD defended	1		
N9: Number of Habilitations to Direct Research (HDR) defended			
N10: People habilitated to direct research or similar	1	1	
TOTAL N1 to N7	**4**	**3**	**1**

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

The research activity of this team is focused on the epidemiology, transmission dynamics and maintenance of West Nile, chikungunya and dengue viruses, which are of great concern for public health in Europe. The activity includes also the evaluation of the potential for epidemic transmission of chikungunya by *Aedes albopictus* under a range of climatic scenarios, the identification of novel strategies for control and the evaluation of the efficacy of the currently available control options in the case of new outbreaks.

The activity carried out at the start of the evaluation period was based on the contribution of a limited number of personnel (specifically 1 professor, 1 technician, 1 post doc recruited for one year and 1 PhD student). Only recently, the team has been reinforced with the recruitment of a new research scientist, new post docs (under recruitment) and a new PhD student.

In term of relevance and originality, the research activity is based on the combination of field-based eco-epidemiological studies and recently with laboratory based models and advanced bimolecular studies (e.g. genotype-by-genotype studies on interaction between DENV and *Ae. aegypti*). The integration of these disciplines has increased the relevance and scientific impact of the more traditional eco-epidemiological studies mostly carried during the first phase of the evaluation period.

The level of scientific production is difficult to evaluate : the number of original publications conducted by the team's leader during the last few years is limited. These publications span from general review articles on journal with low IF. More recently, one young scientist of the team published in highly qualified journals (e.g. PloS Pathogens and PNAS), whose scientific production can be classified as excellent if compared to other young scientists of the institute. However most of these publications are the result of investigations conducted before to join the team. This investigator has obviously the potential, the scientific expertise and the qualifications needed to continue on this path and initiate new projects for the team.

Assessment of the research team's integration into its environment:

In the context of the continuous invasion and spread of exotic vector species in Europe such as *Ae. albopictus* and *Ae. aegypti*, and with outbreaks of mosquito-borne viruses such as West Nile virus and chikungunya, this team can provide advanced expertise and knowledge in terms of vector identification, availability of vector control option and basic knowledge of viral ecology and epidemiology which may be of particular utility for the French public health authorities. The team's leader has proven to be instrumental in initiating and coordinating such projects. Both the team leader and the new young research scientist, in terms of national and international cooperation, appear to be well integrated, due to the number of projects and program and initiatives in which they are involved. The team appear to be active in external fund raising both at EU and non-EU level, although the precise amount of those funds allocated to Pasteur Institute is not specifically reported.

Assessment of the research team's reputation and drawing power:

The team leader served as Scientific Coordinator of the West Nile virus sub-project of EDEN (Emerging Diseases in a Changing European Environment) an EC-funded 6th Framework project, and as a member of the Executive Steering Committee of the entire project. Currently he is scientific coordinator of the Mosquito-borne Diseases sub-project of EDENext, a 7th Framework project. He is also work-package leader in a second FP7 project, DengueTools, and is on the Executive Steering Committee of both projects. The young research scientist has obtained highly competitive funds in the past (2 Marie Curie research fellowship) and has also drawn funds from the American NSF.

Currently the number of permanent staff appears to be very small relative to the research potential of some of the activities carried out by the team. Most of the activities are based on the collaboration and joint projects with external teams and laboratories. Recently new promising activities within the lab have been developed thanks in part to the scientist that joined the team.

Training and teaching is also provided by the team including courses at Intitut Pasteur (*Arthropod Vectors and Human Health*), French universities and international institutions. This activity is of interest and should be recognized. It should also be noted that the Unit is responsible for an archive of insects of medical importance that includes many type specimens and is consulted by entomologists from around the world.

Assessment of the strategy and 5-year project:

The future research direction appears more focused and better described than those carried out in the past.These will be focused on:

- Coordination of the research activities carried out by teams included within the WP MBD of the EU FP7 project EDENext on the ecology and epidemiology of WNV and in particular on winter survival of vectors and the virus, on host specificity of mosquitoes, and on the non vectorial transmission of the virus (host to host) including experimental infection. However, a description of preliminary results already obtained, on the ongoing analysis and on potential publications were not provided.

- Evaluation of the potential for epidemic transmission of dengue and chikungunya in Europe, through studies on the effect of temperature on viral replication, studies on host vector preference and vector competence and vector-virus interaction.

- Assessment of control strategies for Aedes albopictus in the field.

The objectives of these activities appear to be well focused and may produce extremely relevant advances in our understanding on the biological mechanism favoring these MB diseases outbreaks. The possibility to operate within collaborative projects as in the case of EDENext or DengueTools provides the opportunity to combine field and laboratory studies and to produce comprehensive epidemiological models in which all the parameters estimated could be integrated.

Of great public health relevance are also the experiments carried out to control A. albopictus in urban and periurban areas, since to date, in absence of a vaccine, vector control in the environment is essential to reduce or at least mitigate VBD spread.

Conclusions

-Considering the size of the team and the past organization, the performance during the evaluation period was below the expectation in term of scientific publications. The potential to improve this especially after the inclusion in the team of a very promising young research scientist is there. This member has brought into the team innovative tools and vision about future development of the research in virus-vector interactions. The team leader has initiated international collaborations that should provide significant results that could be easily monitored in the next future.

Strengths and opportunities:

The team is involved in EU and extra EU research networks which guarantee the possibility to obtain an impressive amount of data and to validate laboratory model assumptions under field conditions.

The ability to operate in a Department where several other laboratories operate with advanced molecular and technological resources, including planned improvements in informatics, should favor further cooperation and internal integrative programs for combined entomological and microbiological studies.

Weaknesses and risks: The main weakness is that the broad program of activities proposed may decrease the chances of in-depth research on certain aspects and to produce an insufficient number of scientific publications despite the impressive amount of data expected to be generated in the future.

Recommendations: The team is encouraged to improve their publication strategies in journals with higher IF. It is also encouraged for more integrated research plans with other laboratories/ departments at Pasteur Institute.

Team 14: Invasive Bacterial Infections

Team leader: Mr Muhamed-Kheir TAHA

Workforce

Workforce	Number on 30/06/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	1 [0.5]	0	0
N2: EPST or EPIC researchers	0	0	0
N3: Other professors and researchers	2 [1]	3 [2]	2
N4: Engineers, technicians and administrative staff * on a permanent position	5 [1.25]	5 [1.25]	
N5: Engineers, technicians and administrative staff * on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	2		
N7: Doctoral students	0		
N8: PhD defended	0		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	2	2	
TOTAL N1 to N7	11 [4.75]	8 [3.25]	2

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

The output from this team has been of international quality and the number of publications has been good for a group of this size, with papers in leading in field journals including PLOS Pathogens. The group has made important contributions to the introduction of vaccines at a national level and the implementation of a specific vaccine to control an outbreak of disease in Normandy. Their research is original, and they are recognized for their efforts to establish relevant humanized models for pathogenesis of meningococcal infection, and the ability of certain strains to induce host cell apoptosis.

Assessment of the research team's integration into its environment:

The group is also a NRC and a WHO coordinating centre, so they actively contribute to health policy, mainly in the area of vaccine implementation. Research funding of the group has been modest, given that many vaccine companies have been funding reference laboratories to perform epidemiologic studies for vaccine evaluation. There has been a recent award of an ANR grant to study metabolism and virulence (in collaboration with another group) which will support a postdoctoral scientist. The group could benefit from more interactions with other basic research teams at the Pasteur Institute on host cell apoptosis and pro-inflammatory signalling.

Assessment of the research team's reputation and drawing power:

The laboratory is respected at the international level and the head has been invited as an advisor to several vaccine companies and to give some presentations at international meetings. They have recruited two postdocs from other countries. They are involved with a project at the European level, in collaboration with groups at the reference unit in Germany.

Assessment of the strategy and 5-year project:

The plan is logical and relates to work that is ongoing in the group. They plan in depth studies in meningococcal biology which are feasible. There is a concern that the team focuses too much on a single pathogen (which might be dealt with in the next few years with a broadly effective vaccine). It could improve its scientific output by strengthening links between the reference centre activity and basic research. Examples include using sera from vaccines and active surveillance of immunized individuals to detect vaccine escape and changes in populations of circulating strains.

Conclusion:

This is a strong team which has been established at the Pasteur Institute for several years and it hosts the NRC for meningococcal disease. Their future plans build from recently established independent basic research, and address questions of fundamental importance to meningococcal biology and potentially prevention. A potential concern is the focus on a single pathogen that might become less important following vaccine implementation. The group should be encouraged to attract more research funding.

Team 15: Cellular Immunology and Immunogenetics

Team leader: Mr Jacques THÈZE

Workforce

Workforce	**Number** on 30/06/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors			
N2: EPST or EPIC researchers	1	1	1
N3: Other professors and researchers	3	3	3
N4: Engineers, technicians and administrative staff * on a permanent position	2.5	2.5	
N5: Engineers, technicians and administrative staff * on a non-permanent position			
N6: Postdoctoral students having spent at least 12 months in the unit	6		
N7: Doctoral students	4		
N8: PhD defended	6		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	3	3	
TOTAL N1 to N7	**16.5**	**6.5**	**4**

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

Team 15 includes about 10 people (researchers, technicians, postdocs and students); the personnel is divided into two groups that are led by two permanent researchers, (a 3rd group will be created and will take care of an IL-7-based clinical protocol). The team has been able to successfully collect approximately 700K Euros in research grants in the examined period.

The research team focuses on the study of cellular immunity in HIV infection with a particular attention on CD4+ T lymphocytes, as well as on two cytokines: IL-2 and IL-7. The two main avenues of research for the future seem to be concentrated on the design of an IL-7-based clinical trial and on an in-depth analysis of how the immunogenetic correlates with protection from HIV progression in HIV controllers (HIC).The research focusing on the clarification of the IL-7 signal transduction pathway (IL-7 signalosome) is interesting and novel; the portion of the research with IL-2 and HIC is not highly original, with the exception of the results showing that CD4+ T cells of HIC are characterized by a high avidity for HIV peptides. The rationale underlying the IL-7-based clinical trial is novel and interesting but speculative; it is also unclear why the researchers did not try to collaborate with the clinicians that (also in Paris) are currently running phase II/III trials in HIV patients using IL-7.

In the 2007-2011 period the team has generated 16 original papers and 5 reviews in peer-reviewed journals; 7 more papers stemmed from external collaborations. This is not an impressive publication list, although some papers are published in quite visible journals (JI, Plos pathogens, AIDS, JBC).

Assessment of the research team's integration into its environment:

This is difficult to evaluate how the team structures its research collaborations. The team appears to have ties with other HIV researchers, that could nevertheless be made more solid and extensive: 1) the team has produced 7 papers in collaboration with other research teams in the 2007-2011 period but more efforts should be spent in the attempt to expand the pool of collaborators; 2) despite working on IL-7, and even if a major clinical trial that uses this cytokine in HIV-infected patients is ongoing (with some important groups in Paris being part of this multicenter effort), the team did not manage to perform analyses on IL-7-treated patients.

Assessment of the research team's reputation and drawing power:

The head of the team was only invited once to give a talk at an international conference outside France, He also wrote two reviews, and joined a scientific council in the frame of the international network of Pasteur Institute. Nevertheless, the team was able to attract postdocs and PhD students. Ten new collaborators including four from abroad have joined the group in the 2007-2011 period.

The team members participate in three collaborative research projects; these projects nevertheless, are mainly limited to French institutions. The committee recommends that the team should make efforts to extend its collaborations outside Paris and abroad.

Assessment of the strategy and 5-year project:

The main future research avenues develop around three ideas: 1) further analyses on the IL-7 signalosome; 2) an IL-7-based clinical trial and 3) in-depth investigations of how the immunogenetic correlates with protection from disease progression in HIC. The first objective is interesting and original: IL-7 plays a fundamental role in T cell stabilization and homeostasis in a number of infectious, oncologic, and haematologic diseases. The team has performed a lot of work in the attempt to clarify the signalling pathway of IL7; much still needs to be done and should be done as the results are likely to be important far beyond HIV.

The rationale for the IL-7-based trial is based on the assumption that T cell priming in the presence of extremely low viral titers will result in the generation of T lymphocytes endowed with high affinity TcRs: a possible but still speculative event.

As far as idea 3 is concerned, the innovative aspects of the African cohort of HIV-infected children need to be clarified. In the US, a major effort aiming at clarifying the immune correlates of protection against progression to AIDS in Elite Controllers has been undergoing for a number of years with an immense amount of money. The proponent should also be aware of recent data in the literature showing that a number of non-HLA genes are involved in modulating protection against HIV infection and against the progression of disease to AIDS.

Conclusion:

This team, although composed of a group of solid scientists, has moderately performed during the past period, with a rather modest number of papers in not highly visible journals, with a limited number of collaborations and limited involvement in science outside Pasteur, especially abroad.

Strengths: The IL-7 signalosome research is original and potentially important.

Weaknesses and risks: Clinical trials are interesting but speculative. The research of HIC needs to be clarified in more details to avoid the risk of looking like a duplicate of what is performed at Harvard and has been running for quite some years. Additional potential weakness stems from the fact that it is not clear what will happen to the team after its PI will retire.

Recommendations: An effort to expand the collaborations is urgently needed. Literature should be reviewed more carefully and investigators running IL-7 trials in Paris, or elsewhere, should be contacted. The general feeling was that this team has a tendency of being endogamous. They should open up to the world outside Pasteur Institute.

Team 16: Enteric Bacterial Pathogens

Team leader: Mr François Xavier WEILL

Workforce

Workforce	Number on 30/06/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	0	0	0
N2: EPST or EPIC researchers	0	0	0
N3: Other professors and researchers	5 [1]	4 [1.3]	4 [1.3]
N4: Engineers, technicians and administrative staff * on a permanent position	14.5 [0.9]	15.5 [1.9]	
N5: Engineers, technicians and administrative staff * on a non-permanent position	0		
N6: Postdoctoral students having spent at least 12 months in the unit	1 [1]		
N7: Doctoral students	0		
N8: PhD defended	0		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	0	1	
TOTAL N1 to N7	20.5 [2.9]	19.5 [3.2]	4 [1.3]

* If different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

• Detailed assessments

Assessment of scientific quality and production:

The team "Enteric Bacterial Pathogens" represents a reference center as well as a research unit. It comprises the national reference centers in the fields of enterobacteria and Vibrio as well as a WHO collaborating center for salmonellosis. The team handles about 10 000 isolates per year. Over the last years 26 papers have been published by the group. In addition, 18 cooperative papers with major contribution as well as 19 papers with minor contribution have been published. The majority of the papers appeared in very good journals in the field of microbiology. One article in Nature Genetics was published in collaboration. The articles are mainly focused on the epidemiology of enteric pathogens using genome techniques such as MLST and others. Altogether, the scientific quality and the production of the team are very good.

Assessment of the research team's integration into its environment:

The team "Enteric Bacterial Pathogens" collaborates very well with other laboratories not only at the campus but also on a national and international level. The team has contacts with reference centers on Campylobacter as well as on enteroviruses. There could be more collaboration with groups at the campus of the Pasteur Institute. Recently, however, the group initiated collaboration with the platform present in team 2 on the characterization of Shigella dysenteria clones. Furthermore, there is collaboration with the world leading team in the field of microbial epidemiology. The excellent collaboration of this team with other teams is demonstrated by the fact that they were able to respond immediately to the recent E. coli outbreak in Germany with a minor spot in southern France. The team was able to characterize the strains and composed also a paper in an international journal. Furthermore, the team collaborates with other groups in the field of antimicrobial resistance. The team holds grants from different sources; especially the major funding comes from the French Ministry of Health.

Assessment of the research team's reputation and drawing power:

The team has a long and successful tradition at the campus of the Pasteur Institute. The team leader matches this tradition, he is well-known and a leading figure at the national scale and is also well-known internationally. He is invited as a speaker at international conferences, his international reputation is also illustrated by the fact that the laboratory acts as a WHO reference center for Salmonella. Altogether, this team is among the three best groups worldwide working in the field of molecular epidemiology of enterobacteria. As the laboratory is well known as an international reference center it is more difficult to attract PhD students, post-docs and researchers at the international scale. The team, however, participates in national and international research programs. They receive funding from the Bill & Melinda Gates Foundation in a project on typhoid diagnostics.

Assessment of the strategy and 5-year project:

The team developed a strategy for research in the next five years. Into the center of their work they placed the molecular characterization of enteric pathogens with a major focus on enterobacteria as well as Vibrio strains. They use the new genomic techniques including MLST and full genome sequencing. Particular attention is put on the evaluation of antibiotic resistance. Here, the distribution of ciprofloxacin resistance and the characterization of MDR islands represent topics of interest. Furthermore, the team will use the CRISPR locus as a tool for the characterization of enterobacteria. In the field of Salmonella, especially strains of Salmonella kentucky, will be evaluated. The strategy is, from an international point of view, up to date. There are only very few functional studies related to the genome analysis. The team has in mind to analyze the genome sequences in the light of the evolution of pathogens. This is an important topic, nationally and also internationally.

Conclusion:

The team "Enteric Bacterial Pathogens" works very successfully in the field of molecular epidemiology of pathogenic bacteria. They have a particular strength in collecting strains and using genome techniques in order to characterize microbial pathogens. They are well integrated in the field of enteric pathogenesis. As a national reference center the group works successfully at the national and international level. A weakness of their plans is that they do not plan functional studies regarding the biology of their strains. There also could be a better collaboration with other national reference centers in the field of enteric pathogens. There are a number of opportunities, especially in the field of molecular epidemiology where the group should continue to work on national and international networks. The group should also use the competence in the field of enteric pathogens at the Pasteur Institute campus. Furthermore, the group should work on their international visibility.

5 • Grading

Once the visits for the 2011-2012 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).

This score (A+, A, B, C) concerned each of the four criteria defined by the AERES and was given along with an overall assessment.

With respect to this score, the research unit concerned by this report (and, when necessary, its in-house teams) received the overall assessment and the following grades:

❖ Overall assessment of the unit :

Infection and Epidemiology Department

Unité dont la production, le rayonnement, l'organisation, l'animation et le projet sont très bons.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A	A	A	A

❖ Overall assessment of the team : **DROMER-BOURY**

Équipe dont la production et le projet sont très bons. Le rayonnement est excellent.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A	A+	-	A

❖ Overall assessment of the team : **DROMER-BRISSE-CARO**

Équipe dont la production, le rayonnement et le projet sont très bons.

Grading table:

C1	C2	C3	C4
Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A	A	-	A

❖ Overall assessment of the team : **DROMER-CAVAILLON**

Équipe dont la production et le projet sont bons mais pourraient être améliorés. Le rayonnement est très bon.

Grading table:

C1	C2	C3	C4
Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
B	A	-	B

❖ Overall assessment of the team : **DROMER-DOYEN**

Équipe dont la production et le projet sont bons mais pourraient être améliorés. Le rayonnement donne des résultats très insuffisants.

Grading table:

C1	C2	C3	C4
Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
B	C	-	B

❖ Overall assessment of the team : **DROMER-CHIGNARD**

Équipe dont la production et le rayonnement sont très bons. Le projet est bon mais pourrait être amélioré.

Grading table:

C1	C2	C3	C4
Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A	A	-	B

❖ Overall assessment of the team : **DROMER-CHRETIEN**

Équipe dont la production est bonne mais pourrait être améliorée, le rayonnement est non noté et le projet est très bon.

Grading table:

C1	C2	C3	C4
Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
B	NN	-	A

❖ Overall assessment of the team : **DROMER-DROMER**

Équipe dont la production et le rayonnement sont très bons. Le projet est bon mais pourrait être amélioré.

Grading table:

C1	C2	C3	C4
Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A	A	-	B

❖ Overall assessment of the team : **DROMER-FONTANET**

Équipe dont la production et le projet sont très bons. Le rayonnement est excellent.

Grading table:

C1	C2	C3	C4
Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A	A+	-	A

❖ Overall assessment of the team : **DROMER-GOUGEON**

Équipe dont la production est excellente. Le rayonnement et le projet sont très bons.

Grading table:

C1	C2	C3	C4
Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A+	A	-	A

❖ Overall assessment of the team : **DROMER-GUILLEMOT**

Équipe dont la production, le rayonnement et le projet sont très bons.

Grading table:

C1	C2	C3	C4
Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A	A	-	A

❖ Overall assessment of the team : **DROMER-GUISO**

Équipe dont la production et le projet sont bons mais pourraient être améliorés. Le rayonnement est très bon.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
B	A	-	B

❖ Overall assessment of the team : **DROMER-LECUIT**

Excellente équipe à tous points de vue.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A+	A+	-	A+

❖ Overall assessment of the team : **DROMER-MANUGUERRA**

Équipe dont la production et le rayonnement sont bons mais pourraient être améliorés. Le projet est très bon.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
B	B	-	A

❖ Overall assessment of the team : **DROMER-REITER**

Équipe dont la production donne des résultats très insuffisants. Le rayonnement est très bon et le projet est bon mais pourrait être amélioré.

Grading table:

C1 Scientific quality and production.	**C2** Reputation and drawing power, integration into the environment.	**C3** Laboratory life and governance.	**C4** Strategy and scientific project.
C	A	-	B

❖ Overall assessment of the team : **DROMER-TAHA**

Équipe dont la production, le rayonnement et le projet sont très bons.

Grading table:

C1 Scientific quality and production.	**C2** Reputation and drawing power, integration into the environment.	**C3** Laboratory life and governance.	**C4** Strategy and scientific project.
A	A	-	A

❖ Overall assessment of the team : **DROMER-THEZE**

Équipe dont la production et le rayonnement sont très bons. Le projet est bon mais pourrait être amélioré.

Grading table:

C1 Scientific quality and production.	**C2** Reputation and drawing power, integration into the environment.	**C3** Laboratory life and governance.	**C4** Strategy and scientific project.
A	A	-	B

❖ Overall assessment of the team : **DROMER-WEILL**

Équipe dont la production est bonne mais pourrait être améliorée. Le rayonnement est excellent et le projet est très bon.

Grading table:

C1	C2	C3	C4
Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
B	A+	-	A

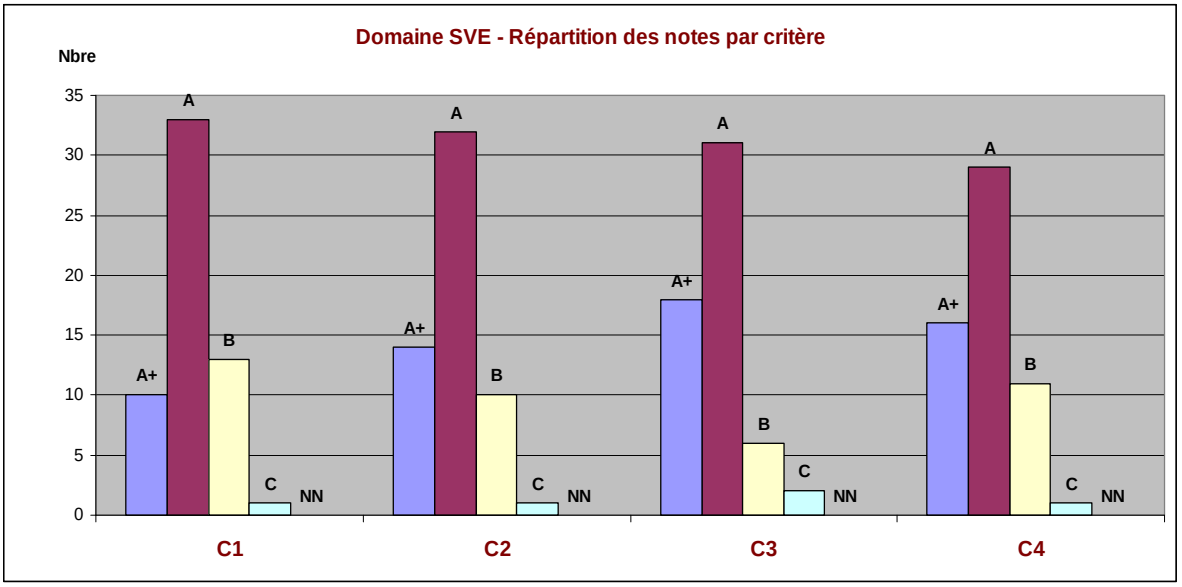
6 ● Statistics per field : SVE au 10/05/2012

Notes

Critères	C2	C2	C3	C4
	Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A+	10	14	18	16
A	33	32	31	29
B	13	10	6	11
C	1	1	2	1
Non noté	-	-	-	-

Pourcentages

Critères	C1	C2	C3	C4
	Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A+	18%	25%	32%	28%
A	58%	56%	54%	51%
B	23%	18%	11%	19%
C	2%	2%	4%	2%
Non noté	-	-	-	-



7 • Supervising bodies' general comments

Institut Pasteur

Centre National de Référence de la Rage

Centre Collaborateur de l'OMS de Référence et de Recherche pour la Rage

Unité
Dynamique des Lyssavirus et Adaptation à l'Hôte
Dr Vét. Hervé Bourhy
Dr Pharm. Laurent Dacheux

Centre de traitement antirabique
Dr Florence Ribadeau-Dumas

Paris, February 20th, 2012

Subject : Comments on the evaluation report by the AERES Site Visit Committee

Dear Sirs,

My team is grateful to the members of the AERES Site Visit Committee for their constructive and positive feedback and thanks these members for their time spent on this evaluation.
However, I would like to rise two comments concerning the report and in particular the conclusion.

1/ two sentences located at one line of interval: [context of the superb facilities of Pasteur Institute] and [some facilities at Pasteur in particular informatics and bioinformatics supports (which are very important for this unit and for other Units) seem to be limited at present] are in contradiction. Furthermore this type of message should be addressed to Pasteur Institute as a whole and not be located in the specific conclusion of the evaluation of the Unit 'Dynamique des lyssavirus et adaptation à l'hôte'.

2/ we are particularly satisfied that the committee underlined the fact that [the unit offers a unique example of integration between] what should be better called the activities of the 'Centre National de Référence pour la Rage' [and fundamental research]. However, the use of the terms [service/or platform] and the sentence [as a general comment, the committee thinks that any platform or service should have fundamental research integrated in it. Absence of research activity has the risk of decreasing the quality of the routine, service work] are misleading. These terms [service/or platform] should not be used to qualify an activity of expertise (that of the 'Centre National de Référence pour la Rage') which has been granted by an open and selective call process and which lead to significant research and publication activities. Furthermore, these general comments, the validity of which I will not comment, should be better placed elsewhere in the general report but not in the conclusion of the report of the Unit 'Dynamique des lyssavirus et adaptation à l'hôte'. It may be seen in contradiction with the very positive message delivered to this unit on that precise matter.

Best regards,

Hervé Bourhy
Head of the Unit 'Dynamique des lyssavirus et adaptation à l'hôte'

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Droit d'accès et de rectification auprès du Centre National de Référence, loi du 06 janvier 1978

Institut Pasteur

Génotypage des pathogènes et Santé publique
Département Infection et Epidémiologie

Paris, February 20th, 2012

We greatly appreciated the efforts of the AERES Committee and its detailed assessment of our activities and projects.

However, we would like to answer to the comment of the AERES Committee "The plan on viral pathogen discovery and detection appears sound and based on innovative methods but less well developed and focussed on demands from other units and the CIBU platform". We feel this comment slightly underestimates our efforts and implication on this topic.

As mentioned in our scientific report, the platform has only very recently accessed to high throughtput sequencing technology through an Illumina HiSeq-2000 sequencer, installed only at the end of 2010 and funded largely through our successful effort to obtain an equipment grant to cover part of the sequencer as well as computing and storage equipment.

Regarding this new activity, our platform has proved to be reactive and fully involved through different actions, in particular our active patnership in the PathoDisc (Pathogen Discovery) program of Institut Pasteur.

Two major applications are proposed to our collaborators: genomic characterization of emerging bacterial and viral strains on the one hand, and detection or identification of novel pathogens in complex samples on the other hand. The platform is also strongly engaged in the development of bioinformatic tools and pipelines for sequence data analysis (currently hosting two bioinformaticians on temporary contracts).

Furthermore, these activities have already been rewarded by three publications in this domain (Cheval et al, 2011 J. Clin. Microbiol.; Sauvage et al, 2011 J. Virol.; Sauvage et al, 2011 Emerging Infectious Diseases).

Institut Pasteur

Génotypage des pathogènes et Santé publique
Département Infection et Epidémiologie

Since 2011, the demand on high throughput sequencing has increased significantly and our platform is involved in many ongoing research programs (PTR, INCA, ANR...).

Besides, in order to better respond to our public health missions, we expect to obtain through the “Grand emprunt" funding frame, a medium-capacity sequencer (MiSeq Illumina, Proton Ion Torrent, or 454 junior..) allowing to increase flexibility and rapid response in case of emergence of pathogens.

To conclude, given that our platform has access since only one year to this new technology, has become dynamically involved and has already developped applications to pathogen discovery, the fact that this activity is described as “less well developed” seem to us to underestimate our strong implication on this important strategic topic.

With best regards,

Sylvain BRISSE
Valérie CARO

Co-directors
Genotyping of Pathogens and Public Health
Institut Pasteur

INSTITUT PASTEUR

Unité de Défense Innée et Inflammation

Inserm U874

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From Michel Chignard

To whom it may concern

Paris, February 16, 2012

Assessment of the research team's integration into its environment

No contact with industrial partner is mentioned.

- The following patent, application number EP10305045.6 in 2010: "Recombinant probiotic bacteria for the prevention and treatment of Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS)", has been licensed to Vithera Pharmaceuticals.

- A 9 months R&D contract was signed with Boehringer-Ingelheim in 2007, for the "Study of the anti-inflammatory effect of xxx in lung mucosa".

- A contract for two years has just been signed with Sanofi-Aventis R&D through a partnership Sanofi-aventis – Aviesan. It concerns: "Etapes précoces des infections systémiques dues à *Aspergillus fumigatus*".

Assessment of the strategy and 5-year project.

Considering that 2 senior scientists are on the leave, the overall unit strategy should be better defined.

- We thought that we clarified this aspect. Of the 2 senior researchers who will be leaving, one (M. Si-Tahar) has not presented any projects so the future plans do not

include him. The other (M. Chignard) who will be leaving in 2 years has presented 2 small projects, *i.e. A. fumigatus* (contract with Sanofi-aventis - Aviesan) and *P. aeruginosa* (international cooperation with a US team).

- See below the "Weaknesses and risks" section in which we comment on the future research plans.

- Of note, the *B. anthracis* project has been dropped.

A more translational orientation should be considered ...sharing data and ideas with clinicians (at least for discussion about strategy).

- This has been done during the past five years. Thus, clinicians have been invited to give a talk and to exchange during our internal weekly lab meetings (to give a few examples : F. Pene (Cochin Hospital), P.-R. Burgel (Cochin Hospital), Z. Xing (McMaster University) , R. Ramphal (College of Medicine, Gainsville, US), C.-E. Luyt (Salpetrière Hospital).

- More importantly, in collaboration with P.-R. Burgel (Cochin Hospital) we published data on bronchial explants of CF patients (see Fig 4 and table 2 supplementary data in Dif *et al.*, Eur Respir J. 2010, 6:1120-1130 (http://erj.ersjournals.com/content/36/5/1120.long).

- Part of our projects concerning the study of the pathophysiology of cystic fibrosis are conducted with clinicians working in different CRCM (Centre de Ressources et de Compétences de la Mucoviscidose) for the collections of patients expectorations *i.e.* P.-R. Burgel (Cochin Hospital), I. Sermet (Necker Hospital), A. Clément (Tousseau Hospital) and D. Hubert (Cochin Hospital). This concern for example an ongoing project on the presence of free flagellin in patient expectoration that can be linked to pulmonary exacerbations.

Weaknesses and risks.

Too many ancillary projects

- The focus of our research is on the pathophysiological mechanisms of lung infections during cystic fibrosis. The different subprojects we proposed are all orientated towards this aim with basic, preclinical and translational approaches.

Thus, knowing that in cystic fibrosis *P. aeruginosa* and *A. fumigatus* are two important colonizing pathogens and that Influenza is a threat, we proposed the following quite well focused subprojects:

Subproject A
-Importance of the Type II secretion system in death due to *P. aeruginosa* lung infections.
-Interactions between *A. fumigatus* and respiratory epithelial cells.

Subproject B
-The roles of TLR9 in *P. aeruginosa*-induced inflammation, cell damage and lung injury
-Expression and roles of AMPs in host defense against bacterial infection
-Interface between basic research and biomedical investigations

Subproject C
-Study of the molecular interactions between alveolar macrophages, lung epithelium and P. aeruginosa, an important opportunistic pathogen in CF and COPD
-Influenza A virus (IAV)-mediated subversion of innate immune anti-microbial responses.

It would be helpful for the future implementation of the AERES recommendations (Weaknesses and risks) to provide us with more specific comments on the above different subprojects.

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to AEREs and members of
the site visiting commitee

Paris, 20th february 2012

Dear Colleagues,

We would like to thank the members of the AERES committee for the pleasant and efficient evaluation conducted. We appreciate the committee's useful suggestions and advice concerning our organisation, research and future developments.

With best regards,

Pr Fabrice Chrétien:

REPONSE de N. DOYEN à AERES

I thank the experts for their positive feeling about our recent achievement and work in progress. They noted for example that "the data are solid and published in appropriate journals, investigating the specificity of the DNA /TLR9 interaction is a solid proposal .. ".

In contrast, I disagree with their remarks on the "unambitious and disorganized character of our work". I think that on the contrary working to mechanisms which are involved in the specific TLR9 interaction with the DNA of different parasite of the trypanosomatidae group is an ambitious goal. The molecular mechanisms by which TLR9 becomes activated or is inhibited are not yet understood. Up to now no information is available regarding nucleotide sequence and cellular events involved in trypanosomatidae recognition by TLR9. There is a consensus on the need of new approaches and studies in the matter as stated in several publications. Among others, we can cite (Latz *et al* 2007, Nat immunol, 8, 772. Bartholomeu *et al* 2008, J. immunol 181, 1333; Wu *et a*l 2010 J. immunol 184, 4338).

The second part of our plan is to determine the role of TLR 9 in different cell types during the infection by *Leishmania major,* using knockout mice for different proteases that will allow to discriminate the impact of macrophages and dendritic cells in immune response. Indeed, nucleic acid recognition by TLR is coupled to stepwise processing by different cathepsins in macrophages (the host cell of l*eishmania)* and by asparagine endopeptidase in dendritic cells (Ewald *et al*, 2011, J. Exp Med, 208, 643.). This point (which was surprisingly not mentioned in the AERES report) is also of large interest and has been granted by Agence Nationale de la Recherche. The two approaches are not disorganized: they are complementary.

The referees regret that we missed the opportunity to use human cells. Our choice to use mice was deliberated, for at least two reasons: availability of experimental leishmaniosis in mice and availability of TLR knockout mice. It would have been highly premature to work strike away on human cells. Nevertheless, as suggested by the experts, a transfer of this study to human cells could be envisaged later after results be secured in mice model.

Concerning my international leading that the referees judged weak, it seems that my current status in Pasteur institute has been misunderstood. I would like to remember that the majority of my carrier was devoted understanding the transcriptional regulation of the immune response genes with a high output of publications. I had to renounce to my subject and I had to start in 2005 a completely new subject, on the immune response to *L. major*. I moved from the Department of Immunology to the Department of Parasitology in the large unit headed by Jacques Louis. This was done with a very small team (myself, one student and a technician). My reconversion requested a tremendous effort. I have achieved my goal in successfully publishing my first article on *Leishmania* immunology in 2009.

In 2008, after the retirement of my PI, I got an independent E3 group, and I had to move once more from the Department of Parasitology to the Department of Infection and Epidemiology, I have been working hard to obtain grants, to teach the new student and technician and to develop the subject. Our results on the role of TLR 9 allowed us to obtain a grant from ANR with a post doc salary in 2012, to study the impact of the processing of TLR9 in immune response to *L. major* and a fellowship from Dim Malinf for a PhD student in 2011. Now with the help of a 3 years PhD student and a 2 years Post Doc fellow we are in a better position to achieve our results during this three next years and I am indeed not in the mood to retire soon.

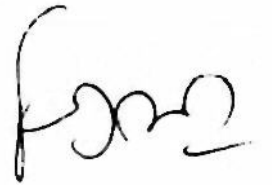
February 20th, 2012

Unité de Mycologie Moléculaire

Centre National de Référence
Mycologie et des Antifongiques

Re : AERES evaluation of the Molecular Mycology Unit, Infection & Epidemiology Department, Institut Pasteur

I have no comment



Françoise Dromer, MD, PhD
Head, Molecular Mycology unit

Institut Pasteur

Unité d'Epidémiologie
des Maladies Émergentes

Rapport AERES Vague C (2013-2017)

Team 7 : Emerging Diseases Epidemiology Unit, Institut Pasteur.

Team leader : Arnaud Fontanet

Observations : Pas d'observation.

Arnaud Fontanet
Chef d'Unité

Le 5 mars 2012

25-28, Rue du Docteur Roux
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Fondation reconnue d'utilité publique habilitée à recevoir dons et legs

INSTITUT PASTEUR

Marie Lise GOUGEON
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Tel 33 1 4568 8907
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Paris, February 22nd 2012

Comments on the evaluation report by the AERES Site Visit Committee.

I wish to thank the AERES Site Visit Committee for the quality of the evaluation process.

Our team is pleased by the very positive evaluation of its accomplishments and research projects made by the AERES Site Visit Committee.

Sincerely yours,

Marie-Lise Gougeon

Chef de l'Unité Immunité antivirale,
Biothérapies et Vaccins

Pharmacoepidemiology and Infectious Diseases unit

Institut Pasteur/UVSQ EA 4499/Inserm U657

Paris, February 21st, 2012

AERES Evaluation Committee

Dear Sirs,

We sincerely thank the evaluation committee for his work.

We do not have any comment.

With many thanks,

Professor Didier GUILLEMOT

Head of the Reseach Group « Pharmacoepidemiology and Infectious Diseases »

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INSTITUT PASTEUR

Unité Prévention et Thérapie Moléculaires
des Maladies Humaines

Paris, February 13th, 2012

Team 10 (N. Guiso) : Molecular prevention and Therapy of Human Diseases

To the members of the scientific committee

The evaluation committee's report largely corresponds to our presentations.

Sincerely yours,

Nicole GUISO
Head of the Molecular
Prevention and Therapy
Of Human Infections

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Marc LECUIT, MD PhD

Microbes and host barriers Group
Institut Pasteur, Inserm

Professor, Paris Descartes University
Division of Infectious Diseases
Necker-Enfants malades Hospital
Paris-F

Paris, le 18 février 2012

To: AERES evaluation committee

I have no specific comment regarding the AERES evaluation committee report on our research activity.

The group and myself thank very sincerely the evaluation committee for their positive evaluation.

Their encouragements are extremely appreciated, and we will do our very best to fulfill their expectations.

On behalf of the members of the Microbes and host barriers group

Marc LECUIT

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Institut Pasteur

Unité « Insectes
et Maladies Infectieuses »

Pr. Paul Reiter
Chef d'unité

16th February, 2012

REITER-observations

- The ETM of five allocated to the Unité restricts us to marginal critical mass.
- With the retirement of our *Ingenieur* we no longer have any technician.
- The workforce reported does not account for the large number of institutes, researchers and students who are supervised from Paris; this is inevitable in field-based projects that include so many geographic regions

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We appreciate that the AERES committee recognized the work of our young group (three years) and that we have achieved "established independent basic research". Several points rose up by the committee that will be considered in our plans for the next period. However, we would like to bring to the attention of the committee several comments:

1- Our report and presentation for the AERES evaluation were mainly based, as recommended, on our "Research activities" during only the last three years since the creation of the IBI provisional Unit. This may have led to the impression of the committee that "strengthening links between the reference centre activities and basic research" are required. Indeed, our laboratory played a major role in reference activities both at the national and international levels that allowed feeding several axes of our research activities (several highly cited papers in the field of typing, antibiotic resistance and vaccine implementations). Moreover, our laboratory has been recently renewed as the Reference centre for meningococci for 4 more years. Indeed, the exploring of "vaccines and active surveillance of immunized individuals to detect vaccine escape and changes in populations of circulating strains" that was recommended by the AERES committee and which figured out in our project, is one of the major terms of reference for in the last three years and for the next period.

2- The Committee underlined that "Research funding of the group has been modest" However, during the last three years two R&D fundings were obtained from two major vaccine companies. We mentioned only consumable funding in our report (51000 euros). However these grants were much higher as they included funding for a technician during 18 months. We are currently in progress to obtain a new 1 year funding from Novartis.

3- The AERES committee also recommended that "A potential concern is the focus on a single pathogen that might become less important following vaccine implementation". Indeed, during the last three years, we focused on one major human pathogen giving the size of our group. This allowed us to "establish a successful independent basic research" as also recognized by the Committee. We agree that we should diversify our research focus for the next period. Indeed, our current research is aimed to understand invasiveness of a bacterium that is usually a resident of the naspophryngeal flora. We have now submitted a research proposal for funding to establish and determine the composition of the human micobiota in the nasopharynx and to establish animal model allowing the study of interaction/interference of different members, including viruses" in the development of invasive infections not only due to *Neisseria meningitidis*,but also other bacteria.

INSTITUT PASTEUR

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February 24, 2012

TEAM 15: CELLLULAR IMMUNOLOGY AND IMMUNOGENETICS
PI: JACQUES THEZE

COMMENTS ON DETAILED ASSESSMENTS BY AERES

In order to put our research into perspective and emphasize the key points of our strategy, I would like to provide some information in addition to the AERES report. The goal here is also to further explain some issues and correct some reviewer comments, particularly on aspects that were not discussed due to a lack of space or time.

Our reply is organized around the Unit's three main avenues of research and takes into account the background of each subject.

IL-7 signalosome in CD4 lymphocytes from healthy and HIV-infected individuals

Because of its importance in i) the central production of lymphocytes, ii) the emergence of the T cell repertoire and iii) the peripheral regulation of CD4 T cell homeostasis, we have concentrated a great deal of effort on studying the IL-7/IL-7R system.

Our huge technical investment in this field means that we are presently one of the most advanced laboratories in the analysis of the IL-7 signalosome. The huge workload this project entailed meant we were unable to publish a large number of papers over this period. As this phase of heavy investment is now over, we are entering into a process of capitalizing on our results, and papers have already been submitted for publication.

We discovered that the IL-7/IL-7R system plays a role in HIV pathogenesis (JH Colle, 2006). More recently, at the molecular level, and for the first time, we elucidated the mechanism of IL-7R defects in HIV-infected patients. This fully validated our hypothesis that the immune system in HIV patients is abnormally activated (D David, 1998). This also explains the irreversible CD4 lymphopenia that is the hallmark of HIV-induced immune deficiency. We chose to accumulate a great deal of data on this subject before publishing, in the hope of reaching a top journal.

AERES recognized the importance of these studies that reach far beyond the HIV field, and all efforts will be made for further development. We are in the process of licensing a number of methods and products before embarking upon industrial collaborations.

HIV controller patients

HIV Controllers (HIC) are an unique group of HIV patients who manage to hold virus replication at very low levels in the absence of any therapy. For the first time, they give us the opportunity to study a human immune system that is able to establish an equilibrium with the virus, and this should point to possible new anti-HIV strategies (therapy and vaccination).

We were among the first to start working on HIV Controllers (HIC), concentrating our studies on CD4 lymphocytes, whereas most other groups focused on CD8 lymphocytes. We were hindered in our efforts by the difficulty of obtaining samples from these very rare individuals, a difficulty our US colleagues did not face. However, and as mentioned by the referees, we nevertheless succeeded in characterizing high avidity Central Memory CD4 lymphocytes (B. Vingert et al. Plos Pathogens, 2010), and additional data on the characterization of the CD4 compartment from HIC will be published.

For the future, as explained to the AERES committee, this avenue of research has been reorganized. The status of HIC infants in Cameroon has been clarified and we henceforth have access to a large number of these individuals. As well as extending some of our previous investigations, much of our effort is deployed to address new questions:
- are HIC resistant to other infectious diseases ?
- do other infections have an incidence on the emergence of the HIC status?
- besides MHC, are other genes involved in the control of the HIC phenotype?

An international collaboration has been set up to study HIC infants. A multidisciplinary team involving more than ten investigators (epidemiologists, pediatricians, virologists, immunologists), seven medical centers and three research institutes, is now operational. This consortium should be able to unravel critical and specific issues that were hitherto out of reach, and place us at the forefront of international competition in HIC studies.

IL-7 therapy of HIV patients receiving anti-retroviral drugs

We have demonstrated that the IL-7/IL-7R system returns to normal after anti-retroviral treatment (JH Colle et al., 2006). This result constituted the fundamental basis of IL-7 immunotherapy as initially proposed by our group (Beq et al., 2004).

A brief reminder of the background to our present study is needed in order to fully appreciate the critical importance of our project. Before launching the first clinical trial of IL-7, our group performed all the preclinical investigations required (in collaboration with Dr Nicole Israël / Prof Françoise Barré-Sinoussi Unit, Prof Jean-François Delfraissy / Hôpitaux de Paris and the Cytheris company). When it was reported that IL-7 induced HIV replication, additional safety studies were necessary and we begun to investigate the means to neutralize this adverse effect. Meanwhile, despite our warnings, a clinical trial of IL-7 was started by others in Paris. As expected, in the absence of additional and intensive anti-retroviral treatment the viral load increased in many patients (Y. Levy et al. JCI, 2009). Even more dramatically, the HIV reservoir was seen to increase (C. Rouzioux, personal communication). ANRS then halted all such clinical trials on IL-7.

Our pilot clinical trial is designed specifically to overcome these difficulties and assess the therapeutic potential of IL-7 in complete safety for the patients. In this context, our

collaborators are newcomers to the field of IL-7 but have a wealth of experience in therapeutic investigations. Our pilot clinical trial has two main endpoints:
- primary endpoint: neutralization of HIV replication after IL-7 injections and the addition of two new and very active anti-retroviral drugs to the standard anti-retroviral regimen.
- secondary endpoint: in-depth analysis of the CD4 T cells produced during IL-7 therapy.
Our main aim is to neutralize HIV replication as an absolute requirement before clinical studies on IL-7 can be expanded. The secondary endpoint is more open. The "new CD4 lymphocytes" that appear after IL-7 cycles will be studied. Obviously, if CD4 T cells with high avidity for HIV antigens are found – as in HIC patients - their protective effects will be tested. Other properties of these CD4 T cells will be investigated (stimulation of CD8s and cells from the innate immunity branch,...).

Our project is adapted to match the context, and involves "selected" collaborators. Among all the properties of the IL-7-induced CD4 T lymphocytes studied, their avidity for antigen is measured. Independently of the results on avidity, all the other investigations performed will provide new and critical data. One may conclude that the speculative part of the project remains very limited. Its most important goal is very realistic.

International Collaborations

Our network of collaborations is efficient, flexible and novel. Since this point was not discussed with AERES experts, we would like to provide a summary of these efforts here:
- in Paris, we take full advantage of the expertise present on the Pasteur campus, but also collaborate with a large number of medical centers. We conduct our studies on IL-7 and HIC as part of large ANRS consortiums and are currently involved in international cooperation to study HIC in Cameroon.
- in Europe, we collaborate with Zeiss and Leica. This places the Unit at the forefront of imaging approaches.
- in the US, we interact with the Ragon Institute, which is affiliated with the Harvard Medical School. A review was recently written (J. Thèze et al. 2011) with researchers from this Institute and a collaborative project is under discussion. Collaborative work is also conducted with the Benarroya Institute in Seattle (B. Vingert et al. 2010).

Since 2002 we organized an HIV/AIDS think tank to which recognized leaders are regularly invited for purposes of presenting results and hypotheses before publication. Prospective debates are also frequent events in the think tank. Our Unit is therefore part of a continuous interactive process involving many laboratories and medical centers internationally recognized for their work in HIV research.
Web site: http://www1.pasteur.fr/recherche/GRS/accueil.html

In addition to the meetings indicated in the summary sheet, members of the Unit have presented their data at many others international conferences.

Altogether, we hope to have demonstrated that "the spirit of the Unit" is far from being endogamous.

Administration
As discussed with "Institut Pasteur" management, all projects take account of PI date of retirement.

Alain ISRAËL
Directeur de l'Evaluation scientifique
Institut Pasteur