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

Department for the evaluation of
research units

AERES report on unit:

Department of Cell Biology and Infection

BCI

Under the supervision of the following
institutions and research bodies:

Institut Pasteur

Institut Nationale de la Santé Et de la Recherche
Médicale - INSERM

Centre National de la Recherche Scientifique - CNRS



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

Department for the evaluation of
research units

*On behalf of AERES, pursuant to the Decree
of 3 november 2006¹,*

- Mr. Didier HOUSSIN, president
- Mr. Pierre GLAUDES, head of the
evaluation of research units department

On behalf of the expert committee,

- Mr. Moshe OREN, chair of the
committee

¹ The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n° 2006-1334 of 3 November 2006, as amended).



Evaluation report

This report is the result of the evaluation by the experts committee, the composition of which is specified below. The assessments contained herein are the expression of an independent and collegial deliberation of the committee.

Unit name:	Department Cell Biology and Infection
Unit acronym:	BCI
Label requested:	
Present no.:	
Name of Director (2013-2014):	Mr Jean-Christophe OLIVO-MARIN
Name of Project Leader (2015-2019):	Mr Jean-Christophe OLIVO-MARIN

Expert committee members

Chair:	Mr Moshe OREN, The Weizmann Institute, Israel
Experts:	Mr Alain CHARBIT, Université Paris Descartes (Representative of INSERM CSS)
	Mr Guy CORNELIS, Unité de recherche en Biologie des Organismes, Belgium
	Mr Pier Paolo DI FIORE, IFOM-IEO, Italy
	Ms Claire FRANCASTEL, Université Paris-Diderot (representative of INSERM CSS)
	Mr Jonathan HOWARD, Instituto Gulbelkian de Ciencia, Portugal
	Mr Didier LERECLUS, Unité MICALIS-GME (Representative of INRA)
	Ms Jennifer LIPPINCOTT-SCHWARTZ, National Institutes of Health, USA
	Mr Paul MANGEAT, Macromolecular Biochemistry Research Center (Representative of CoNRS)
	Mr Roberto MAYOR, University College London, United-Kingdom
	Mr Cesare MONTECUCCO, University of Padova, Italy
	Mr Richard MOXON, Weatherall Institute of Molecular Medicine, United-Kingdom (Representative of the Scientific council of the Pasteur Institute)
	Mr Jacques NEEFJES, The Netherlands Cancer Institute
	Mr Raimund OBER, The University of Texas and Dallas, USA
	Ms Ana POMBO, Max Delbrück Center for Molecular Medicine, Germany
	Mr David SIBLEY, Washington University School of Medicine in St-Louis, USA



Scientific delegate representing the AERES:

Mr Jean-Antoine LEPESANT

Representatives of the unit's supervising institutions and bodies:

Mr Christian BRÉCHOT, Institut Pasteur

Mr Laurent KODJABACHIAN, CNRS

Ms Stéphanie POMMIER, INSERM



1 • Introduction

History and geographical location of the unit

The Cell Biology and Infection department was created in 2002 with the goal of integrating cell biology, infectious diseases, and microbiology into the common framework of cellular microbiology, and interfacing the latter with hard sciences including physics, mathematics and computer science. While the department has promoted the interdisciplinary concept of cellular microbiology at the international level, it has also addressed topics related to cellular dynamics during cell life and death and during the development of important pathologies affecting humans. The department is presently spread over seven buildings located on the campus of the Institut Pasteur in Paris. The successive chairs have been Mr Philippe SANSONETTI (2002-2005), Ms Pascale COSSART (2006-2009) and Mr Jean-Christophe OLIVO-MARIN (2010-2013).

Management team

The department is managed by a chair and a co-chair, assisted by a Department council composed by the PIs of the units and platforms, and representatives of the different categories of personnel (scientists, ITA, secretaries, laboratory helps, students, postdocs). The council comprises various sub-committees (seminars, meetings, training) and liaisons (informatics, industry). The council holds 4 meetings per year, where different matters related to the scientific and organizational aspects of the department are discussed and recommendations can be made.

AERES nomenclature:

SVE1 LS1, LS2, LS3, LS4



Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	10	8
N2: Permanent researchers from Institutions and similar positions	47	33
N3: Other permanent staff (without research duties)	35	27
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	1
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	66	44
N6: Other contractual staff (without research duties)	14	12
TOTAL N1 to N6	173	125

□Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	30	
Theses defended	32	
Postdoctoral students having spent at least 12 months in the unit*	59	
Number of Research Supervisor Qualifications (HDR) taken	4	
Qualified research supervisors (with an HDR) or similar positions	25	21



2 • Overall assessment of the unit

The committee evaluated a total of 10 research units plus 1 group with a 5-year contract (G5 group) and one technology platform, the imaging platform, whose head is also carrying out independent research.

The committee was impressed with the very high quality of the research performed by all the units that it reviewed. All of them are doing world-class research that is in the forefront of their respective fields. Several of the more senior unit heads are unquestionably world leaders in their fields, and some of the younger unit heads are already enjoying a strong international reputation and are well positioned to become world leaders. Therefore, it is fair to say that this is an outstanding department by all international standards, and the committee wishes to congratulate the Pasteur for nurturing such a strong center of scientific excellence.

Strengths and opportunities related to the context

Scientific quality and outputs: the department is performing highly competitive research in important areas of cell biology, molecular biology, infectious diseases and cancer research. The results of this research are being published in top journals, both high impact general audience journals and the highest ranking more specialized journals. The department is employing cutting edge methodologies, particularly in bio-imaging, and is also contributing to the development of novel breakthrough methodologies.

Academic reputation and appeal: the department includes several “stars” of high international reputation, who are among the top worldwide in their fields of research. These individuals are keynote speakers in major meetings and recipients of prestigious awards, adding strong academic reputation. For young researchers - post-docs and PhD students - who are interested in those particular areas, working in one of these world-leading laboratories is a very appealing possibility. Younger PI’s in the department are also well known in their respective fields, with increasing international reputation and appeal.

Interaction with social, economic and cultural environment: PIs and team members within the department are actively involved in a variety of society-benefiting activities, including popular science lectures to the public, serving on public committees and more. Several PIs are also actively involved in collaboration with companies and are therefore potentially contributing to economic development.

Organisation and life: the department is well organized, and has regular department-level activities such as joint seminars. The impression of the Committee was that, in general, both the senior and the junior members of the teams are happy and proud of being in the department.

Involvement in training through research: the department offers high-level training to post-docs and PhD students. In many of the units, particularly the larger ones, there is internal organization into several research teams, each led by a more junior director, which ensures close supervision and training of post-docs and students.



Weaknesses and threats related to the context

Change of leadership: the most imminent threat to the department is the fact that three of its prominent leaders, which at present contribute to its high visibility and international reputation, are expected to reach retirement for one of them next year, and for the two other in about 4 years. Replacing them with scientists of the same high calibre is not going to be easy. It will be important to make sure that the best choices of next generation leaders are made; otherwise, the department may lose its leadership position in these highly competitive areas.

Coherence and internal collaborations: at the start of the review process, the committee had some uncertainties about the degree of coherence within the department and among its different teams. In particular, it was unclear to what extent the department insists on research that is directly related to infectious diseases, as opposed to basic cell biology research that does not try to link with infectious diseases. However, upon completing the review process, the committee was positively impressed by the fact that almost all the basic cell biology researchers in the department have at least some interface with infectious diseases and infectious agents. In general, there are many collaborations within the department, which benefit from the unique juxtaposition of researchers with complementary expertise. A few units, however, are less engaged in such collaboration, and unit heads should be encouraged to look actively for additional collaborative opportunities within the department. In a few cases where collaboration appears to be less than optimal, one obvious reason may be the physical fragmentation of the department: its units are spread all over the campus, and some units are relatively isolated in as much as the presence of neighbouring units of the same department is concerned.

Recommendations

An obvious potential threat to the international prominence of the department is the fact that several of its best-known and most influential scientists are about to retire in the near future. The department should strive hard to maintain a continuity of excellence. This should be done by making every effort to ensure that new units are headed by researchers who are at the same level of competence and creativity as those that are about to retire. Therefore, it is advised that decisions about the heads of new units should be reached only after a very rigorous evaluation. Researchers from within the Pasteur and those from outside should be given equal opportunity to apply for each open unit head position, and quality should be the cardinal basis for making the final choice.

The committee strongly encourages the acceleration of the forthcoming relocation of all department units under one roof or at least within neighbouring buildings only.

Many researchers within the department are employing very advanced methodologies that are at the cutting edge of their field. The highly sophisticated methodologies require highly sophisticated research staff that will be able to make the most out of the advanced platforms available in the department and at the Pasteur in general. In addition, these advanced platforms generate a lot of complicated data, and highly qualified personnel is needed in order to process this huge amount of data. There is therefore a need to enable the recruitment of several additional people that will relieve this bottleneck.



3 • Detailed assessments

Assessment of scientific quality and outputs

The research performed in the department is very diverse, and covers a broad spectrum of topics and scientific sub-disciplines. In fact, several of the units are performing multidisciplinary research on a regular basis. Yet, the department has several specific research areas on which it is particularly focused and in which it has reached substantial prominence. These areas include pathogen-host interactions (mostly bacteria, but also viruses), intracellular trafficking, signal transduction and transcriptional control, as well as advanced microscopy and image analysis.

Members of the department carry out highly original research in their prospective fields. Over the last 5 years, this has given rise to a series of breakthrough discoveries that have significantly advanced biological research. Their findings are having broad impact not only on their own work, but also on that of many other researchers worldwide. This is reflected by an impressive number of publications in high impact journals, including general audience journals such as *Cell*, *Science* and *Nature*, as well as the top specialty journals in their respective fields, such as *Nature* family journals (*Nature Cell Biology*, *Nature Methods*, *Nature Structural and Molecular Biology*), *JCB* and others. These papers are often highly cited, and several of the unit leaders have exceptionally impressive numbers of citations and H index. Even the younger and perhaps less prominent members of the department are highly productive and are generating top-quality science. The committee could not identify even a single unit that was underperforming or not highly competitive in its field. The department should definitely be congratulated on being able to maintain such high standards throughout all its units.

In sum, the department is carrying out very original, cutting edge work at the highest international standards, and its work is very well received and noted worldwide. It is undoubtedly one of the strongest biological research departments in France, and among the top in its field in Europe in general.

Assessment of the unit's academic reputation and appeal

The members of the department generally have high academic reputations in their respective fields, which altogether contribute to the high reputation of the entire department.

Members of the department were and are involved in many large-scale, multi-partner national and international projects, including the coordination of several EC projects and networks, as well as a substantial number of national projects. They are also playing leading roles in technology-based networks for development of novel technologies as well as applying them towards additional uses.

The post-docs and students are of high international standards, as revealed by the outstanding research presentations given by many of them during the committee's visit and the ensuing discussions.

Members of the department have received many awards and others tokens of international and national recognition. Among these are several very prestigious prizes for the leading PIs, as well as highly competitive, prestigious grants at both senior and more junior levels, including an impressive number of ERC grants and top-end grants from international organization such as HHMI.

Members of the department are on the editorial boards of many journals, including some of the most prestigious journals in their fields of research.

Members of the department are frequently invited to lecture at international meetings, including highly noted forums such as Gordon Conferences and Keystone Symposia, and have also presented many keynote lectures in important meetings. Naturally, the more senior and better known PIs have a particularly strong record of international invitations, but many of the younger PIs are also accumulating impressive lists of invited talks.

Members of the department are invited to contribute reviews to top journals, both in their specialty fields and in more general readership forums. Examples include reviews in *Cell*, *Nature Reviews in Cell Biology*, *Nature Reviews in Microbiology*, *Nature Reviews in Cancer*, and many more.



Members of the department serve on important local, national and international committees (e.g. President of the INSERM committee on Genetics, Development and Cancer, SAB of the Basel Biozentrum, President for fundamental research of the Scientific Council of the Belgium Cancer Foundation, member of the Scientific Council of the Ville de Paris).

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

The research performed in the department is mostly focused on fundamental biological questions, and as such its extension into collaborations with industry and other commercial entities is relatively limited. Nevertheless, some of the units are also involved in more easily-applicable research, and have various levels of collaboration with non-academic entities (e.g. a promising collaboration with big pharma on Nemo inhibitors, collaboration with software developers).

Assessment of the unit's organisation and life

Despite the large diversity of research areas, the department is organized in a coherent manner. There are many internal collaborations among the different units of the department; one obvious benefit is that, even in highly competitive areas, department researchers can identify unique questions that put them at advantage over their competitors, owing to the synergy with other experts within the same department. The combination of cutting edge cell biology and imaging methodologies with fundamental questions in microbiology is particularly evident throughout the department, and is a distinctive feature of the work being done by the department members.

Resources are generously shared, and are the basis for many collaborative studies among department members.

The atmosphere in the department is positive, and members at all levels appear to be happy with their environment and their interactions with other members of their own units as well as of other units with whom they have contact.

Assessment of the unit's involvement in training through research

Training of post-docs and students is at a high level, and they are given ample credit by the unit heads. This was evident from the fact that the vast majority of presentations to the committee were delivered by post-docs and students, as well as by junior team leaders. The quality of training was reflected by the quality of these presentations, as well as by the ability of the post-docs and students to conduct perceptive, very well informed discussions with the committee members and the audience.

Members of the department are involved in dissemination activities and outreach to both the scientific community and the general community. These include several courses and lecture series organized within the Institut Pasteur (e.g. a school in cell biology), as well as national and international advanced training programs (e.g. directing a series of international EMBO courses in Spetses, Greece, organization of EMBO courses in South Africa).

Several members of the department hold active teaching positions in higher education institutions, such as École Polytechnique, Palaiseau.

Assessment of the strategy and the five-year plan

To the best of the committee's understanding, the department as a whole does not have a 5-year research plan. This is understandable in view of the large diversity of research topics and sub-disciplines within the department, and is consistent with academic freedom of the individual unit leaders. The committee can therefore relate only to the strategy and research plans of the individual units.

Overall, the committee was impressed with the originality, quality and scale of ambition of the proposed research. There are many cutting edge projects in the pipeline, and their successful execution will ensure that department researchers maintain their high international visibility and impact on their respective fields. Assessments of individual research plans are provided in the following sections.



One important comment regarding general departmental strategy has to do with the fact that several prominent PIs are expected to retire within the coming few years, and their units are bound to be closed. This will create open slots for the establishment of new units. In view of the need to maintain the high profile and international competitiveness that the department presently enjoys, it is crucial to ensure that the new unit leaders will be of the same calibre as those whom they replace and those who are presently heading the other successful units. This will necessitate a very careful and rigorous selection process. Furthermore, once the new units are established, they should be provided with the best means to enable them to make rapid progress and increase their international visibility and appeal, taking advantage of the intellectual input and technological infrastructures available in this excellent department.



4 • Team-by-team analysis

Team Bacteria Cell Interactions Unit

Name of team leader: Ms Pascale COSSART

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	2	2
N2: Permanent EPST or EPIC researchers and similar positions	10	8
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	12	12
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	25	23

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	5
Theses defended	1	2
Postdoctoral students having spent at least 12 months in the unit	8	7
Number of Research Supervisor Qualifications (HDR) taken	1	1
Qualified research supervisors (with an HDR) or similar positions	4	6



• Detailed assessments

Assessment of scientific quality and outputs

The unit studies the interactions between *Listeria monocytogenes* taken as a model pathogenic bacterium and eukaryotic cells. The Science carried out in the Unit is at the forefront of knowledge in Cellular Microbiology, using the most up-to-date technology.

The unit investigations follow four main axes:

- I) transcription and translation regulation in *Listeria* during cell infection;
- II) cellular interactions of the various effector proteins secreted by *Listeria* in vivo;
- III) epigenetics impact of *Listeria* on the host cell;
- IV) impact of Lactobacilli on oral infection by *Listeria*.

A non-exhaustive set of sub-projects is outlined here below:

The first theme of research led to the discovery of a link between virulence and metabolism, of the concept of "excludon" and of a riboswitch that controls an anti-sense RNA rather than a mRNA.

The second theme led to the identification of six new *Listeria* virulence factors, of a new role for clathrin, septins and the PI5Pase OCRL, and to the observation that *Listeria* induces a global de-SUMOylation through the indirect action of listeriolysin O (LLO). LLO was also shown to induce a transient mitochondrial fragmentation.

In the third theme, the unit demonstrated that LLO induces histone H3 dephosphorylation, activation of caspase 1 and the inflammasome as a result of K⁺ efflux. The unit also showed that *Listeria* infection is favored by deacetylase SIRT2 that deacetylates histone H3 on the promoters of a subset of genes. SIRT2 ^{-/-} mice were more resistant to *Listeria* infections, showing that an epigenetic mechanism imposed by the pathogen may contribute to pathogenesis. In the same theme, the unit showed that *Listeria* protein LntA is a nucleomodulin, which remodels chromatin during infection.

To study the impact of Lactobacilli on the oral infection by *Listeria*, a gnotobiotic humanized mouse model was used. Lactobacilli decreased *Listeria* systemic dissemination and changed the intestinal expression of a subset of genes, particularly interferon-stimulated genes (ISGs). Lactobacilli also reshaped the *Listeria* transcriptome.

A senior member of the unit has made an important contribution to the study of a secreted bacterial factor (LntRA) that reaches the nucleus and remodels the chromatin of the infected cell by interacting with the heterochromatin-inducing protein BAHD1. The LntA-BAHD1 interaction modulates the expression of a new immune network, the type III interferon pathway. This work which has led to publications in PNAS, Science and PLoS one, has significantly contributed to the outstanding record of the unit.

The publication record is breath-taking with 35 original articles signed as first or last author (~ 1 publication per year and per scientist) including 12 papers in high profile "generalist" journals such as "Science", "Nature", "Cell", "Cell Host and Microbe" and "PNAS". Besides these primary articles, the unit published a considerable number of reviews (> 25) in the best journals (Nature review of microbiology, Cell, PNAS, Cell Host Microbe...). The total scientific production of the unit, including at least one member of the team, is 127 articles in 6 years.

It is worth noting that the four lines of research generated publications of the highest level, showing that they are all equally successful and outstanding.

Assessment of the team's academic reputation and appeal

This unit is among the founders of the discipline "Cellular Microbiology"

The head of unit is a world opinion leader who received during the 6 last years numerous prestigious international awards: Balzan prize, 2013; Helmutz fellow, 2013; Van Deenen medal, 2011; Robert Kock medal, 2011. A member of the unit is member of the national academy of sciences in Costa Rica. Another member received the René Descartes prize in 2010.



During the period under review, the head of unit was a member of numerous scientific advisory boards, like the SAB of the Biozentrum in Basel (CH).

Since 2008, the unit is involved in 16 international or national research programs and is coordinator of six of these programs.

The unit has been extremely successful in the acquisition of national and international prestigious research grants from institutions like the HHMI and the ERC.

The head of the unit has been a driving force in the creation of this successful department at Pasteur and is or has been serving Science in many international boards, including at EMBO to cite only one. She should be warmly congratulated as an outstanding scientist and unit administrator.

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

The work of the unit is focused on basic research and no major recent collaboration with industry is reported.

Assessment of the team's organisation and life

Members of the team were highlighted in the presentation and given the chance to present their own work.

The head of unit is very sensitive to the issue of the future of each of her long-term collaborators.

Assessment of the team's involvement in training through research

A high number of PhD and Master's students have been trained by this unit.

For several cycles, the head been responsible for the international EMBO course on Infection biology organized in Spetses (Greece).

The unit participates to the organization of the General Microbiology course of the Institut Pasteur. Moreover, a senior member of the unit is Professor of Microbiology at the university Paris 7 since 2010. Other members of the team provide a contribution to teaching.

Assessment of the strategy and the five-year plan

The head of unit will retire in four years from now and the unit will be closed down. Until that time, research will go on, pursuing the ongoing work and collecting the fruits of the several "omics" efforts that have been done over the recent years. There is no doubt that the level of innovation and publication will remain very high.

The head of unit should be congratulated as a mentor and group leader for the way she takes care of the future of all her collaborators.

Conclusion

▪ Strengths and opportunities:

The unit is among the very best and most renowned ones of the Institut Pasteur. The activity has been at the same time focused (on Listeria) and impressively diverse in the aspects studied.

The international reputation is as high as it can be.

▪ Weaknesses and threats:

The head is meant to retire in the next few years and the unit will be closed down, which will be an enormous loss for the Department and for the Institut Pasteur.

The question of the relocation of the personnel is expected to be solved in a smooth way.

▪ Recommendations:



Maintain the level of innovation and excellence which are the hallmarks of the team.

Team Biology of Cell Interactions unit

Name of team leader: Ms Alice DAUTRY-VARSAT

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	2	1
N3: Other permanent staff (without research duties)	2	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)	1	1
TOTAL N1 to N6	6	4

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	2



• Detailed assessments

Assessment of scientific quality and outputs

Important findings have been made on the unique endocytosis pathway used by IL2R and the ability of Shigella to alter host receptor recycling and Golgi biogenesis.

Excellent progress has been made on understanding the biology of Chlamydia focusing on TTS substrates and their role in altering host biology.

Progress has been made using heterologous expression to tag Chlamydia proteins and study their trafficking in host cells, including the identification of 7 proteins that are targeted to the nucleus.

Excellent papers have been published in top journals in microbiology (such as Infect Immun., Traffic, PLoS Pathog, Cell Host Microb., Cellular Microbiol.), and although promising, the work has not yet reached the level of general interest journals.

Assessment of the team's academic reputation and appeal

The unit leader is a highly regarded researcher in cell biology and in intracellular adaptation of Chlamydia.

The junior scientists in this group have begun to gain some visibility by being invited to present seminars in the EU.

The major success for external funding is acquisition of a junior ERC grant. The unit is also supported by several smaller ANR grants.

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

The head of the laboratory has until recently been the general director of the Institute Pasteur. In this role, there have been many achievements that enhance the visibility of the institute and provide important social and economic contributions.

The work of the unit is focused on basic research and thus far, this has not lead to partnerships with industry

Assessment of the team's organisation and life

The plan for junior scientists to progress in their individual careers was very clearly presented and logically explained.

Members of the team were highlighted in the presentation and given the chance to present their own work.

Assessment of the team's involvement in training through research

A number of PhD and Master's students have been trained by this group and excellent papers have been generated by these individuals.

Scientist in this group have been involved in teaching at courses offered in Paris Universities, IP, and EMBO, including master's degree program.

Assessment of the strategy and the five-year plan

The primary project presented was the continuation of the work on how Chlamydia alters host cell signaling, trafficking and metabolism. Excellent biological leads have been discovered in the prior period and these will now be prioritized for further study.

One of the challenges going forward is deciding how to balance the various pathways being studied (trafficking, nuclear function, or metabolism) in order to make mechanistic advances without efforts becoming diluted.



The research plan is ambitious, but focused on key pathways that are altered by Chlamydia infection.

Plans for incorporating new genetic techniques need to be carefully considered as there will be challenges with importing these new technologies.

Conclusion

▪ Strengths and opportunities:

The team has made excellent progress on the identification of bacterial effectors that act on host pathways including chromatin modification, ubiquitination, and metabolism.

The development of genetic systems by others has opened up new avenues to study the biology of Chlamydia, which continues to be an important pathogen.

▪ Weaknesses and threats:

The genetic tools needed to make mutants are not yet available in this system, yet they are likely to be developed soon. As this team is not at the forefront of the development of this technology, it will be key to develop the right collaborations.

▪ Recommendations:

It would highly advantageous to recruit a top postdoc with skills in molecular genetic of bacteria to enable this team to take advantage of these developments in a timely manner.



Team

Pathogénie Microbienne Moléculaire

Name of team leader: Mr Philippe SANSONETTI

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions (incl.engineer)	5	5
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	16	14
N6: Other contractual staff (without research duties) : technicians + secretary	5	4
TOTAL N1 to N6	27	24

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	12	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	3	4



• Detailed assessments

Assessment of scientific quality and outputs

The team runs a large activity aiming to understand the host cell response to Shigella infections and the way Shigella manipulates the host cell biology. It is one of the few teams able to combine top fundamental research and a research line aimed at translating the finding in the laboratory to ways to control infections.

The team is running a large EU network and -with Industry- aims to develop a vaccine against Shigella infections that reached Phase I/II trials at present. He is further developing synthetic vaccines for this purpose in collaboration with chemists.

The team is a leader in the field and its research is at the Frontiers of Science. The team is leader in:

- I) the development of the colon microbiome,
- II) the role of infections in stem cell development, and
- III) many aspects of this highly important field in cancer, auto-immunity and infection biology.

The team has many publications in highest ranking journals such as J. Exp. Med. 2008; Nature 2010; 2 Cell Host and Microbes (2011, 2012).

Assessment of the team's academic reputation and appeal

The team leader has the highest international scientific reputation (obtained two consecutive ERC advanced grants), runs an EU network on vaccine development and is involved in various editorial boards. He also runs a teaching program on infectious diseases at the Collège de France

The team is a lead partner in networks, infrastructures or centres with numerous Collaborative international programs: Labex IBEID (integrative biology of emerging infectious diseases). Two senior scientists of the unit have obtained important grants : (STOPENTERICS Vaccination against Shigella and ETEC : 800 K / 12 M€. Aviesan / BioAster. "T3SS: prévention et traitement des infections bactériennes à Gram négatif. 1 M €).

An impressive number of post-doctoral students have been recruited and are currently present (15 present each year). This is a very attractive unit for foreign post-docs with own support. International environment.

Mr Philippe SANSONETTI has been awarded numerous prestigious prizes during the last five years: GSK Foreign scientist of the Year Award, ASM/AAM (2009) Fellow to the US National Academy of Sciences (2012), Grand Prix INSERM de l'Excellence Scientifique (2012), Senior International Research Scholar Program of the Howard Hughes Medical Institute. He has editorial activities for multiple high ranking journals.

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

The team uses and/or develops the latest technologies (high throughput analyses, imaging, stem cell biology, systems biology, analyses of the microbiome in the crypts, epigenetics and many more).

The team leader has a long standing legacy with an established school on microbiology and research on host-pathogen interactions. He is one of the founders of this field. Also many groups came from his lab. He founded the Department de Pathogénie Microbienne Moléculaire at Pasteur which is one of the best Departments at Pasteur.

The team leader has organized several prestigious Conferences (e.g. Gordon Research conference, "Microbial adhesion & Invasion", Newport, 2005; EIMID annual meeting, Arc & Senans, France, 2008 ; "The Microbiota", Collège de France, Paris, 2011 Interacademic symposium: "The New Microbiology", Académie des sciences, Paris, 2012. He has set up interactions with industry, Danone, Sanofi, Merieux.

The team is also strongly involved in translational research (vaccinology, developing innovative immunomodulatory molecules ,...).



Assessment of the team's organisation and life

This is a strongly organized team with host-pathogen interactions as a leading theme. PhD student and post-docs were very happy about the research and support by the team leader.

The team leader presented the fruits of the team-work which was impressive and outstanding and illustrates the contributions of the various members of the team

The team has excellent accessibility to pooled resources.

Assessment of the team's involvement in training through research appeal

The team comprizes two senior researchers, both highly involved in training of undergraduate and PhD students. One is director of the Teaching Department at Institut Pasteur since 2010; he has trained eight PhD students. The second has trained many PhD and Post-docs: 3 PhD students (1 ongoing) and 5 post-doctoral fellows (2 ongoing). Mr Philippe SANSONETTI received an ITN Marie Curie for 2013-2016.

Assessment of the strategy and the five year plan

The team will pursue highly original and groundbreaking projects but based on own original research.

There is a great consistency of the proposed projec with clear plans and future outlook.

There is an excellent credibility of the strategy as recently valued by a second ERC Advanced grant.

The team was successful in the past during the development of the various exciting new plans. The five-year plan will open new and exciting lines of research aimed at studying the microbiome in intestinal crypts, bacterial-host interactions. It is anticipated that this work may also provide clues on the origin of diseases like Crohn's disease and cancer.

These projects will be supported by an ERC senior fellowship (starting January 2014) and during the 2014-2019 period by ERC 2- DECRYPT 2 500 000 €, as well as by numerous other financings : PTR, ANR, DIM, FRM, ERA-Net, ARC, Merieux, Sanofi, Aviesan....

Conclusion

▪ Strengths and opportunities:

This is an excellent team with excellent plans based on excellent work. Many groundbreaking discoveries are expected and the research on the microbiome in crypts may become textbook knowledge with high relevance for cancer and Crohn's disease.

▪ Weaknesses and threats:

No weaknesses detectable. Only point will be plans for retirement (planned in 2020) and the potential follow-up of this great research.

▪ Recommendations:

The research of the Mr Philippe SANSONETTI's team is top world class and it is one of the most visible and best research lines at Pasteur. The committee was impressed by the exciting prospects of the future research presented. Mr Philippe SANSONETTI has a clear idea about his research and is also successful in finding and obtaining external funding. As mentioned above, the achievements of the unit had a determining impact on the very high international standing of the Department of Cell Biology and Infection and hopefully this will continue in the coming years.

There was no possibility to test the quality of the various subgroups within the team. Yet, none of these appear to present the wide overview and vision of the team leader. This implies that Mr Philippe SANSONETTI is imperative for the successful continuation of this research line. This is important for the coming years (as Mr Philippe SANSONETTI expressed his retirement in August 2020). The transition period should be discussed in due time if this highly successful and visible line of research is wanted to continue after his factual retirement.



Team

Nuclear Organization and Oncogenesis

Name of team leader: Ms Anne DEJEAN

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	6	6
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	8	11
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	15	18

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	5	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	2	2



• Detailed assessments

Assessment of scientific quality and outputs

Ms Anne DEJEAN earned her international reputation by discovering the PML-RAR translocation in leukemia and elucidating the functions and regulation of PML and PML-RAR in normal and cancer cells, where she has established herself as one of the international leaders of the field. More recently, the main research interest of the team has shifted towards the study of Sumoylation, as well as of molecular mechanisms that regulate cellular senescence.

The team was one of the pioneers in studying the roles and regulation of Sumoylation, and she has maintained a leading position in this field. While in the early days of the field there was only limited interest in Sumo, in recent years the field has seen rapid growth, because many important proteins have been found to be functionally regulated by this modification. Over the years, the unit has made a number of seminal discoveries relating to the role of Sumoylation in cellular senescence as well as in control of cell proliferation and apoptosis.

The present research deals primarily with the biology of Sumoylation, and is based primarily on genetically modified mice generated in the unit, which allow to obtain reduced levels or complete absence of Sumoylation in the whole body or in specific organs. This is based on manipulating the levels of Ubc9, the E2 enzyme of the Sumoylation pathway. The analysis of these mice has revealed new links between Sumo and innate immunity, response to viral infection, intestinal stem cells and intestinal tissue homeostasis. These findings are innovative and exciting. Moreover, they provide opportunities for strong collaborations within the Pasteur Institute, and indeed such collaborations are already beginning to take place, and have provided a very recent exciting result showing that Ubc9^{+/-} mice are hypersensitive to Shigella infection.

Another avenue pursued by the unit aims to map the Sumo landscape on chromatin. This is presently being done by 2 parallel approaches: analysing the distribution of Sumo on chromatin by Sumo IP, and assessing the distribution of the Sumoylation machinery by ChIP against specific E2 and E3 enzymes from this machinery. The first approach is particularly challenging; nevertheless, the unit researchers have already succeeded to obtain very interesting results, and a first paper appeared recently in Genome Research. The new unpublished data on the impact of sumo on the regulation of histone gene expression, where a detailed molecular mechanism is already being elucidated, is actually more exciting. Overall, the present work of the unit may be opening up a new area of research in transcription regulation.

In addition, the Dejean team is closely collaborating with the Bischof team on the study of mechanisms of cellular senescence. This close collaboration has already led to several notable publications in high profile journals, and is highly likely to continue to yield important results and additional publications in top journals.

Overall, the team has an outstanding publication record, with a total of over 15,000 citations. In the last 5 years, the work of the unit has been published in very high profile journals, including Nature Cell Biology, Genome Research, Gastroenterology, PNAS, EMBO J and Mol Cell Biol. In addition, the unit leader established strong collaborations, which led to authorships in high impact journals including Nature, J. Exp. Med, Genome Research, PLOS Pathogen. Judging from the recent unpublished work, one may expect a wave of high profile, high impact new publications within the coming couple of years.

Assessment of the team's academic reputation and appeal

The team leader is among the most internationally renowned scientists at the Pasteur Institute and a world leader in the study of Sumo biology. She has received numerous international awards in recognition of her outstanding achievements, including the Prix ARC-Leopold Griffuel and, most notably, the L'Oréal-UNESCO prize in 2010. She is actively involved in important national and international committees: notably, she was President of the INSERM committee on Genetics, Development and Cancer in 2008-2012, and is currently President for fundamental research of the Scientific Council of the Belgium Cancer Foundation. She is also involved in public science-related activity, and is presently a member of the Scientific Council of the Ville de Paris. In addition, she has been invited to speak in many national and international meetings.

The unit has attracted a substantial number of post-docs and graduate students.



The unit leader has authored invited reviews in high profile journals; most recently, she has contributed an invited review to the prestigious Nature Rev. Cancer. In addition she obtained the highly prestigious ERC advanced grant.

In conclusion, the unit has outstanding academic reputation and appeal.

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

The L'Oreal-UNESCO Prize has exposed the research of the team to a wide audience of non-scientists. Several projects of the team have potential implications for the development of anti-cancer drugs, but the committee is not aware of any active partnership that is presently going on with a non-academic entity on such projects.

Assessment of the team's organisation and life

The unit is well organized, and the different research projects are well coordinated and work in complementation and harmony. There is extensive cross-interaction between the Dejean team and the team of O. Bischof, which contributes to productivity. The members of the unit appear happy with the atmosphere in the unit. Several of them were given the floor to present their work, and it was clear that they are enthusiastic about their research and are receiving much credit from the unit head for their achievements.

Assessment of the team's involvement in training through research

The post-doc and PhD student who presented their work during the review process were knowledgeable and delivered sophisticated, impressive presentations. This attests to the high quality of the research training that they are receiving.

Assessment of the strategy and the five-year plan

The future plans of the unit are based on their published and unpublished recent achievements. They are original and creative.

In the next five years, emphasis will be placed on understanding the roles of Sumoylation in the regulation of chromatin function and gene expression, as well as on following up the exciting new findings on the role of Sumo in innate immunity, stem cells and tissue homeostasis. These are all worthy projects, with great potential for innovation and with ample preliminary data that support the chosen directions.

Conclusion

- **Strengths and opportunities:**

The unit is performing high quality research and has maintained outstanding international leadership and visibility. Recent findings are highly original and open new avenues for clinically-relevant research. The research plans for the next 5 years are exciting and have the potential to lead to important new insights.

- **Recommendations:**

The Dejean team is performing outstanding research in an important area, in which they are considered among the world leaders. Sumo biology is rapidly gaining broad recognition and prominence. Sufficient resources should be allocated to allow the team to remain in the forefront of this highly competitive area.



Team : Molecular and Cellular Biology of Senescence and Age-Related Pathologies

Name of team leader: Mr Olivier BISCHOF

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	1	2
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	3
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	3	6

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

Mr Oliver BISCHOF joined the laboratory of Ms Anne DEJEAN as in 2000, after a first post-doc in the laboratory of Judy Campisi, who is broadly considered as the world leader in the study of cellular senescence. In 2004 he was promoted to CR1, and in 2013 he was promoted to DR2.



Since his arrival to the Pasteur, Mr Oliver BISCHOF has been focusing on the mechanisms of cellular senescence, with particular emphasis on the roles of PML proteins and sumoylation in this important process. This direction was a natural combination of the expertise that he acquired in the Campisi lab and the specialization of the Dejean lab, and Mr Oliver BISCHOF has been very successful in maximizing the synergy between these areas of research in order to obtain significant novel insights. This started already with his first publication from the Pasteur (Bischof et al, EMBO J. 2002), and continued with a constant flow of original studies published in high profile journals. In the last several publications, Mr Oliver BISCHOF was already the senior author, attesting to his leadership role. The most notable highlights in the last 5 years include elucidation of the role of TBX2 in PML-induced senescence (EMBO J. 2011), and particularly his Nature Cell Biology paper (2012) showing the involvement of Ago2 and miRNAs in the silencing of proliferation genes in senescence - a very original and innovative study. Very recently, he identified a major role for a lncRNA (PANDA) in regulation of senescence; this is also a groundbreaking study, presently under revision for Nature Struc. Mol. Biol.

Overall, the Bischof team has an excellent publication record, which documents several highly significant and original research achievements. Considering the small size of the team, this is very impressive.

Assessment of the team's academic reputation and appeal

The team has gained considerable academic reputation as an original contributor to the study of cellular senescence. This is reflected in several invited talks in international meetings, including an invited talk at a Keystone Symposium in 2011, as well as several excellence awards. It is expected that with the increasing interest worldwide in cellular senescence - a rapidly growing "hot" area- and Mr Bischof's continuous contributions to this area, its international reputation and appeal will continue to grow.

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

The committee did not have specific information on that aspect.

Assessment of the team's organisation and life

The team is in close interaction with the larger team headed by Dr. Anne DEJEAN. There is extensive cross-interaction between the two teams, which contributes to productivity. The Committee was impressed by this very positive spirit of collaboration and interaction.

Assessment of the team's involvement in training through research

Mr Oliver BISCHOF has personally supervised several post-docs and has led them to very successful research outcomes. The combination of his high scholarly capabilities, impressive technological knowhow and pleasant personality, make Mr Oliver BISCHOF a natural excellent mentor for training young researchers.

Assessment of the strategy and the five-year plan

In their proposed research for the next five years, the team aims to undertake an integrative functional analysis of non coding RNAs and chromatin dynamics during senescence. The work will involve a combination of cutting edge methodologies, some of which are already in operation in the team and some that will be established and optimized during the coming 5-year period. The plan is ambitious, but not unrealistic. Interest in cellular senescence is rapidly growing, but comprehensive molecular understanding is still greatly lacking. The planned project has good potential to provide groundbreaking information in this direction and to increase the international visibility of the team and of the Pasteur Institute in this area. In order to maximize the impact of this ambitious plan, Mr Bischof should be provided with the ability to recruit new competent members to his team.



Conclusion

- **Strengths and opportunities:**

The team is performing high quality research in an important and rapidly growing area of biology and biomedicine. The research plans for the next 5 years are exciting and have the potential to lead to important new insights.

- **Recommendations:**

Mr Oliver BISCHOF is very competent and has a strong track record. His proposed research is timely and relevant. Therefore, he should be encouraged to develop his own independent leadership position, increase his team, and pursue the resesarch directions proposed by him.



Team

Dynamics of host Pathogen Interactions

Name of team leader: Mr Jost ENNINGA

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)	0.5	0.5
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	3.5	3.5

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	1



• Detailed assessments

Assessment of scientific quality and outputs

The originality of this team lies in two domains: the chosen research enterprise itself, the determination to analyse the earliest events in the interaction between an intracellular parasite and its host cell with the highest possible resolution in time and space and the development of refined analytical methods for the revelation and interpretation of these events.

The research is marked by exceptionally imaginative technical developments that are enabling for this and other research enterprises that demand such high time and spatial resolution. The team is making a lot of new findings and will make a lot more. One example is the role of the Rab11 sorting endosome compartment in the dismantling of the *Shigella* phagosome membrane. Another is the energising of bystander cells by intracellular infection of their neighbours, resulting in a distinctive transcriptional signature.

The work of the team is well-cited in the field. The field of intracellular host-pathogen interaction is exceptionally difficult at this level and not many people work in it. The work is technically very beautiful and much praised.

The team leader is a scientist at an international level, as can be seen from the international journals he publishes in and the list of invitations to present his work at international fora. The team publishes in the best journals in its field, *Cell*, *PLoS Pathogens*, *Cellular Microbiology*, *Nature* journals etc.

Assessment of the unit's academic reputation and appeal

The team collaborates extensively in house with technical development teams in advanced microscopy and has contributed to successful grant applications for state of the art microscopy instrumentation. The team collaborates also extensively and creatively with a group at the Weizmann Institute in the use of a Focused Ion Beam scanning electron microscope.

There are post-docs and students from excellent international environments with extremely high standards of intellectual excellence (Israel, Portugal, Germany etc) funded with individual fellowships (eg EMBO

The team leader himself has received a number of accolades: Studienstiftung des deutschen Volkes, FRM, EMBO and HFSP post-doctoral fellowships, The Robert-Koch-Postdoktoranden Preis, Berlin, FSER Prize and ERC starting grant. The students and post-docs have received a number of personal awards.

The team leader reviews for journals of the highest quality. He and his colleagues participate in numerous conferences, national and international, relevant to their work. Mr Jost ENNINGA himself is invited very widely.

A distinguished level of reviewing activities of the team leader in the last few years: Institut Pasteur representative for the work group "screening" of the Excellence, Initiative IRT-Bioaster (Institut de Recherche et Technologie). Committee member INSERM, recruitment of staff scientists and evaluation (CR and DR), section CSS3 (Cell Biology), 2012-2017, Committee member AERES, evaluation of the CNRS unit UMR144, Institut Curie, November 2012

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

Mr Jost ENNINGA is above all renowned for the elegance of the methods he has developed for imaging very small and fast biological processes in real time. Two of these stand out: the use of the tetracycline system to image type III secretion in real time, and the use of the beta-lactamase system in conjunction with microscope or FACS to enable direct timing of the breakdown of the *Shigella* phagosome. The basic methods existed but the team special skill is the exploitation of these methods for its programme. The team has also more recently developed what appears to be a very efficient method for single-cell transcriptomics. The publications which contain these method developments are highly cited, perhaps more for the biological discoveries they enabled than for the methods themselves.

The team publishes in journals with high impact and relevance, for example *Nature Methods* for the type III story, and *PLoS Pathogens*, an open access journal, for the phagosomal breakdown story.



A number of productive collaborations have been initiated with microscope development and image analysis software colleagues. An important collaboration has also been initiated with the Weizmann Institute in the combined use of CLEM with Focused Ion Beam Scanning Electron Microscopy, a very powerful combination for looking in detail at small complex 3-dimensional structures in cells. Important developments in academic research favour both partners. Success with development work enriches all scientists with problems that might be amenable to such techniques.

Assessment of the team's organisation and life

The accessibility of pooled resources is outstanding.

This is a very young team, started in January 2013. Presently it reflects the dynamic influence of the head of the team. However the team leader has exceptional younger colleagues (see below) with whom creative interactions and novel initiatives are expected to develop.

The unit is well-funded and well run with regular internal scientific meetings .

Attractive, informative web site, not completely up to date (still refers to G5 group) but publications up to 2013.

The team is uncomfortably positioned with separation of office and lab space.

Assessment of the team's involvement in training through research

It is exceptionally good as shown by the list of opportunities offered to students to present their work in national and international fora. During the interview, the team leader took only about 20% of the available time, leaving the remainder to presentations from 3 of his students. All were extremely impressive. These are top quality students thriving in a top-quality environment.

Follow-up of doctoral students: Too early to comment. Internal discussions within the group include a journal club.

The team leader has received an Habilitation to advise Ph.D students in 2009 at University Paris 7. The team is Groupe d'accueil for universities Paris 6 and 7.

The team leader is extremely active in advanced training programmes nationally and internationally. He is especially engaged with training in South Africa, practical and teaching courses including organisation and teaching in 3 EMBO courses in S. Africa. He has supervised several Master students at levels 1 and 2.

Assessment of the strategy and the five-year plan

The programme consists of three research axes (1) the process of vacuolar rupture in *Shigella* (2) vacuolar rupture in other organisms and its relevance to antigen processing and presentation (3) signalling due to vacuolar rupture and host transcriptional response. All of these axes are subdivided into specific work modules. The programme is very well articulated and its general feasibility is not in question.

The project is highly original and very well-defined. It aims at producing a complete description at the molecular and cellular level of all the processes involved in the early entry and accommodation of intracellular pathogens to the cellular microenvironment. The originality lies in the intensity and clarity of the focus, as well as in the technical virtuosity that is brought to bear on the problem, always striving for higher and higher temporal and spatial resolution. There will be successes and failures, but for the moment it is clear that the opportunities for success far outweigh the risks of failure.

Originally conceived as a programme relating to *Shigella*, the phenomena the team is looking at and the techniques and approaches it is developing can be immediately generalised to other organisms. The team has already demonstrated this in the context of vacuolar breakdown by extending the approach from *Shigella* to *Mycobacterium* and is beginning to use *Salmonella* for other purposes. Scientists working on early steps in intracellular infection will profit from these ideas and experiments. The technique for single-cell transcriptomes is generalizable outside host-pathogen contexts.



The team collaborates very effectively with expert microscopists at Pasteur and Weizmann institutes. There is an excellent and productive collaboration with a team on antigen processing and presentation. There is advanced technique development in the context of Euro Biolmaging

The team leader has many effective collaborations and is known for the openness of his personality. He is immediately responsive to technical developments, applies them effectively to his work.

No SWOT analysis reported.

Conclusion

▪ Strengths and opportunities:

Outstanding energy and creativity of the PI, exceptional students and assistants, well-articulated research plan, excellent funding, excellent research infrastructure and colleagues. The team will achieve a far more detailed understanding of pathogen-host interactions during intracellular infection, with a realistic hope for the identification of new drug targetable and steps in pathogen colonisation. It will also provide exceptional training for young scientists, providing them with unusually rich career opportunities. International renown of the team will enhance the world-wide reputation of the Institut Pasteur.

▪ Weaknesses and threats:

These are hypothetical at present, but may become relevant. The fascination for virtuosity in the development of new refined techniques entails the risk of competing for the ability to produce new biological insights. This has been said of the team leader before, but it can be considered as more a routine critique. The reality is that he makes new biological findings wherever he goes and, at least for the time being, everything he touches turns to gold.

The lab has a very broad reach and it is likely that there will be competitors, none probably thinking as broadly and creatively, who will have successes in parts of his programme. The lab has grown very rapidly: there is a risk that this fresh growth may overwhelm the team leader powers to control it adequately.

▪ Recommendations:

The correction of the poor Lab/Office layout should be considered.

The recruitment of a skilled data analyst should be a priority.

Set the present size as the upper limit on the lab for at least three years.

Support the installation of a Focused Ion Beam/SEM set-up at Pasteur.



Team

Cell Polarity, Migration and Cancer

Name of team leader: Ms Sandrine ETIENNE-MANNEVILLE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)	1,25	2,5
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2
N6: Other contractual staff (without research duties)	1	
TOTAL N1 to N6	7,25	7,5

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	1



• Detailed assessments

Assessment of scientific quality and outputs

The team works on the interplay between cell adhesion and migration. The team leader, Ms Sandrine ETIENNE-MANNEVILLE, has found that cell polarity is controlled by cell-cell adhesion and that this polarity plays an important role on directional cell migration. She has made important contributions to the field of cell polarity/migration that are likely to have a broader impact on cancer invasion.

The science developed in this group is top quality and the team has managed to address very important problems of cell biology, such as the interaction between different cytoskeletal components during cell polarization. Particularly exciting are the recent discoveries related to the recycling of N-cadherin during cell polarization and the role that intermediate filaments have in this process.

The publications (notably several in J Cell Biol) are highly cited and are having a wide impact on the field.

Assessment of the team's academic reputation and appeal

The team is internationally recognised as can be concluded from a large number of invitations to talk at international meetings, such as Gordon Conferences, EMBO meetings, Royal Society meetings, etc. Ms Sandrine ETIENNE-MANNEVILLE has been invited, in average, to 5 international meetings per year. Furthermore, in the last five years she has been invited to write 12 reviews in prestigious journals such as Ann Rev Cell Dev Biol, Curr Opi Cell Biol, Curr Opi Neurobio, etc, and in addition she has contributed with chapters to two books. The team and its leader have an outstanding academic reputation.

Assessment of the team's organisation and life

The unit is organized in a very focused and efficient manner. The level of interaction and distribution of different jobs among members of the team seems to be excellent. This highly efficient organization has led to a very high productivity in terms of publications, and at the same time it is possible to sense a friendly and relaxed environment within the team. The team leader has managed to reach the right equilibrium between efficiency and adequate mentoring.

Assessment of the team's involvement in training through research

The team leader is involved in teaching and training at different levels at the Pasteur Institute and in collaboration with other institutions. She is professor at the the École Polytechnique, Palaiseau, France, which allows her to be involved in several additional teaching initiatives. She has been involved in training at national and international courses.

From the presentations during the meeting and from interactions with the students it was concluded that the supervision of students was excellent, as well as the level of mentoring of students and postdocs. No major problem was detected in the interaction within the team and a very positive atmosphere was observed.



Assessment of the strategy and the five-year plan

The trajectory of the team in the past five years has been outstanding and it is expected that it will continue to a very high level in the future. The main topic of the team is adhesion, polarity and migration, and this topic will continue in the future. However it is proposed to expand and move into slightly different areas: intermediate filament and cancer invasion. The intermediate filament area is the natural continuation of previous work and it is expected to be equally successful, although some technical limitations to study these cytoskeletal elements could be found. The second project is related to cancer invasion and it is different from the previous work done by the team. In spite of possible risks, it is likely that these projects will generate important data in the field of cell migration and polarity.

Conclusion

▪ **Strengths and opportunities:**

This a strong and unified team adequately led by Ms Sandrine ETIENNE-MANNEVILLE. The quality of the science is outstanding and it is expected that it will be even better in the future.

▪ **Weaknesses and threats:**

The interactions between this team and other members if the CELL BIOLOGY & INFECTION DEPARTMENT are scarce.

▪ **Recommendations:**

It would be desirable to increase scientific interactions as they could be of mutual benefit. The physical isolation of this team from the other members of the department could explain the reduced level of interactions.



Team Cell signaling and activation

Name of team leader: Mr Alain ISRAEL

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	
N2: Permanent EPST or EPIC researchers and similar positions	10	
N3: Other permanent staff (without research duties)	6	
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	17	

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	7	



• Detailed assessments

Assessment of scientific quality

The unit studies mechanisms of signal transduction and signal regulation in several experimental settings (detailed below) of great relevance both to physiology and to the understanding of human diseases, including cancer, viral infections, and inflammation. The science is of very high level and at the forefront of the fields of investigation.

The unit investigations follow three main directions: (I) analysis of the NF- κ B pathway; (II) analysis of the Notch pathway; (III) structural studies of NEMO and related proteins. A fourth direction, concerning phosphatases, is carried out by an associated group.

The various lines of investigation led during the last five years to some extremely relevant results including:

- the identification and characterization of Ub-related machinery (conjugating enzymes and de-Ub) involved in the regulation of Notch;
- the identification of the regulation of Notch by the kinase AAK1;
- the characterization of the role of OPTN in HTLV1-mediated activation of NF- κ B;
- the characterization of the binding specificity of the Ub-interacting domains in NEMO;
- the discovery of the pathogenetic relevance of alterations of HOIL-1 and LUBAC, and of the ensuing defect in the formation of linear Ub chains, in human diseases.

All this research should be considered of the highest level, and in some cases paradigm-breaking, as exemplified by the recent work on the selective impact of NEMO in signaling pathways.

The publication record is outstanding. Numerous papers were published in the last five years, including several in high profile journals such as Nat Immun, Mol Cell, PNAS, JCB, PLoS Biol and EMBO J.

Assessment of the team's academic reputation and appeal.

This unit has contributed immensely to the field of signaling and has pioneered work on the NF- κ B pathway and on NEMO.

The head of unit is a recognized world leader in his fields of expertise, as also witnessed by the extensive networks of formal connections that he established, contributed to establish and/or fostered at the EU level.

The unit has been very successful in the acquisition of national and international research grants.

The head of the unit has been a driving force in the creation of this successful department at Pasteur and in establishing its reputation worldwide.

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

One of the groups of the unit is involved in a very promising program aimed at the identification of chemical inhibitors of NEMO. This program is well financed by Pharma.

Assessment of the team's organisation and life

Members of the team were highlighted in the presentation and given the chance to present their own work. The head of unit is very sensitive to the issue of the future of each of his long-term collaborators

The figure of the head of this unit represents clearly the added value. It is evident that his vision pervades the work, the integration and the harmonization of the various subgroups. While he has left ample margin for personal development of the pivotal figures in his lab, working as a good mentor for them, his input is clearly evident in all phases of work, especially in designing a unitary vision for the various experimental efforts being actuated in the group.



Assessment of the team's involvement in training through research

A high number of PhDs and Master students have been trained by this unit.

The head of unit has also been involved at the apical level in a vast training program, at the EU level, through the RUBICON network.

Assessment of the strategy and the five-year plan

The head of unit will retire soon, therefore a general evaluation of future plans cannot properly be put forward. However, the pipeline of the lab appeared promising and bound to produce results for years to come.

Assessment of the strategy and the five-year plan

- **Strengths and opportunities:**

The unit is among the very best and most renowned ones of the Institut Pasteur, characterized by a high level of productivity, innovation and originality.

The international reputation of the unit head is outstanding.

- **Weaknesses and threats:**

The imminent retirement of the Head will represent a substantial loss for the Department and for the Institut Pasteur. It is unclear whether the present team leaders within this unit will be able to maintain this very high international level of scientific performance in the absence of the unit head.



Team

Quantitative Image Analysis Group

Name of team leader: Mr Jean-Christophe OLIVO-MARIN

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	9	6
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	14	11

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	5	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	7	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	1



• Detailed assessments

Assessment of scientific quality and outputs

The research addresses important problems in the analysis of imaging data arising in the investigation of biological, mostly cell biological, problems. Modern imaging technologies, especially microscopy experiments produce large and complex sets of data. The information contained in these data sets can often only be evaluated with sophisticated approaches. Unfortunately, the development of image analysis approaches has not kept up with the advances in microscopy and cell biological experimentation. Due to the nature of the data and the complexities of the underlying biological problems, elementary approaches are often not sufficient to extract the biological information that is 'buried' in the data. Therefore there is a major need for the development of fundamental methodologies for the analysis of such data sets. It is this field that this unit is working on.

The work of the group is outstanding. For example, the approaches to the tracking of subcellular dynamic processes are deep and far reaching. There are many ad hoc approaches that are published by others. In contrast, the research of this unit attacks the problems by building deep mathematical foundations and as a result the group's research will have long lasting impact. This fundamental research is complemented by the development of an extensive software platform that is sorely needed in the community and very well received. In addition to the research that originates in the unit itself, the research group also has an impressive list of ongoing research projects, where they use their image analysis expertise to provide critical and non-trivial input to biological projects of colleagues at the Institut Pasteur and elsewhere.

There are very few, if any other groups worldwide that combine this level of fundamental development in the setting of a cell biology department, with the important work on concrete biological problems.

Assessment of the team's academic reputation and appeal

The team has an outstanding reputation in the field, as exemplified by speaking engagements at international conferences and institutions. It should also be pointed out that the unit head has been awarded the status of Fellow of the IEEE in recognition for his outstanding research.

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

The team leader has been playing important roles in international and national research organizations. This has provided important service to the community but has also brought major benefits to his home institution, for example, through the interactions in the project Carnot and the France-Imaging and Euro-Imaging projects.

Assessment of the team's organisation and life

Not assessed since there was no opportunity to interview the group members regarding the life of the team. The organization of the team is very appropriate and effective.

Assessment of the team's involvement in training through research

The unit has a superb track record of education as evidenced by the very quality publications that resulted from the work of the students and post-docs. The presentations given to the committee by the group's members were very impressive and showed a deep understanding of the field by the junior members of the group.

Assessment of the strategy and the five-year plan

The proposed plan for the next phase consists of elements that are natural continuations of successful existing projects and the addition of novel ones. For example, their new project on the development of new algorithms for the evaluation of structured illumination algorithms fills a major void in the understanding and analysis of structured illumination experiments. The original developments in this field relied on analyses that did not account fully and with appropriate theoretical tools, for the stochastic nature of the acquired data. Since microscopy is a technique that, unfortunately, is plagued by very low stochastic signals in the presence of noise, stochastic based analysis tools are critical to adequately analyze such experiments. Major improvements in the experimentation using structured



illumination algorithms can be expected from this work and have already been shown in early results. The proposed work on compressed sensing has the potential to provide the basis for path breaking new microscopy experiments by providing insights into which data should to be acquired and which data can be omitted in order to extract the important information from the data. A further important project seeks to determine the surface geometry of cells in 3D by using an active contours approach. This is highly innovative and promises to provide important new tools for the analysis of cell-cell interactions.

An important continuing project is that of the development of the 'Icy' software platform. The best algorithms and analysis tools are not very meaningful to most members of the biology community if they are not provided in a form that is easily useable. This is especially the case since most cell biology groups do not have the in house expertise to write software themselves. Given the complexity of microscopy data, a powerful software platform is a highly non-trivial exercise in software design and programming. Therefore efforts such as 'Icy' are very much welcome and necessary.

Conclusion

- **Strengths and opportunities:**

In summary the unit has been evaluated to operate at the highest international levels.

The proposed projects are outstanding and will allow the unit to continue the highly productive research that is at the forefront internationally.

- **Recommendations:**

The very important project related to the development of the software platform 'Icy' would benefit significantly from the addition of further staff for the software development aspects of the project.



Team Imaging and Modelisation

Name of team leader: Mr Christophe ZIMMER

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	4
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	5	7

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended		
Postdoctoral students having spent at least 12 months in the unit	6	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	1	1



• Detailed assessments

Assessment of scientific quality and outputs

Mr Christophe ZIMMER, a physicist by training, has made significant contributions in our understanding of how the genome is folded inside the eukaryotic nucleus and in applying advanced computational methods for advanced imaging. Using these methodologies, advanced computational imaging and polymer modeling approaches, recognized internationally as outstanding, his team has produced formal descriptions of the positioning of chromosomes and single genes in the cell nucleus of yeast, a small and tractable system to address the complexity of genome positioning. [Developing this work in yeast, to begin with is intelligent, as the nucleus of yeast contains approximately as much DNA as a human chromosome.]

Early during the period under review, the team established a quantitative description of chromatin positioning in the nucleus of yeast cells using advanced and high-throughput imaging and, importantly, image analyses. Elsewhere in the world, others have produced high-throughput genome-wide mapping of chromatin associations, using chromosome conformation capture (HiC), a population-average approach. Other groups produced ad-hoc observations that some genes appeared non-randomly positioned next to the nuclear periphery, and from these observations conclude that such proximity was enforced by specific and 'functional' cellular mechanisms. Nevertheless, the team single-handedly realized that such an apparent non-randomness of gene positioning could be established by broader constraints to chromosomal positioning, instead of a 'so-called' functional association. So without having previous connections with main players in the field of chromatin architecture, the team was able to make unique and timely intellectual and practical contributions by realizing what might be very simple principles of chromatin organization in the yeast cell nucleus.

In the area of imaging, the team has brought to the Pasteur Institute advanced imaging approaches that rely on 'computational imaging' which require advanced computational processing of imaging information. In this area, the committee observed a genuine intent to reach out and make these highly advanced and relatively unique approaches. It also became clear that there is a significant bottleneck in devising tailored-made computational pipelines for each specific project required by other Pasteurians.

In the period of this review, the team has published in top journals. Of note, a computational model has been published in *Current Biology*, which is an outstanding feat to bring a heavily mathematical piece of work to a mainstream Biology journal. In *PNAS*, they published both on the topic of nuclear constraints of chromatin positioning and on super-resolution of visualization of the *in vivo* cell biology of HIV. In *Nature Methods*, they published another two papers one in nuclear organization and the other in image processing using QuickPALM. QuickPALM was the first widely accessible software package for the analysis of superresolution microscopy data that was computationally very efficient and reduced the time taken to produce a superresolution image by a significant amount. They also published with collaborators (e.g. in *Nature Cell Biology*, and many other publications, e.g. *J. Cell Biol*), including reviews in various topics (e.g. in *J. Cell Biol*). Clearly the team is able to maintain a steady and high-level contribution in both its main areas of research, both within its own program and with collaborators.

Assessment of the team's academic reputation and appeal

The team is involved in several collaborative grants (eg Equipment mi-lourd program, 416K euros to his laboratory), as well as in its own funding (eg FRM, 299K euros), often as a coordinator (ANR, 294K euros to his laboratory).

The team recruits impressively good staff from the best labs around the world (e.g. an investigator previously at NIH), and its alumni reach excellent positions (e.g. a now Junior PI at UCL, UK).

Mr Christophe ZIMMER has had several invited presentations during the period of the review (12 international and 18 in France), although it is not clear how many are invited local seminars or invitations to speak at conferences. No prizes are indicated. Several personal funding awards were gained by members of the lab. It would help the lab's international visibility to increase attendance at conferences.



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

During the site visit, it became very clear that the team leader feels the responsibility to give access to the community to the high-end approaches that the team develops. This is evident in many collaborations within the Pasteur Institute and elsewhere, which not only provide access to available technologies, but also procure funding for increasing local imaging opportunities (Nanopole, ect..)

Assessment of the team's organisation and life

The team organization is outstanding. Top scientists in the relevant, yet highly specialized fields from everywhere in the world are recruited. There is a request for a full time programmer to fulfill reaching out commitments for project-tailored data analysis, in particular from collaborators and a request for appropriate environment to host computer servers and data transfer.

Assessment of the team's involvement in training through research

Nine Master students have had internships. Several recruitments are ongoing for postdoctoral, PhD and Master students.

Teaching for Doctoral School Frontieres du Vivant.

Assessment of the strategy and the five-year plan

The team leader has been positioning his lab to make seminal contributions in the future, by developing in parallel quantitative approaches to measure genome architecture in single cells and to model this information to reach a deeper mechanistic understanding of the principles of genome function. There are excellent collaborators in the Biology field to help achieve these aims.

Conclusion

▪ **Strengths and opportunities:**

The projects are internationally competitive, and this laboratory is one of the international leaders in understanding chromatin organisation in the yeast nucleus.

▪ **Weaknesses and threats:**

The possible threat for the research program is that they may spend too much time helping others and in this way decrease their competitiveness in their two fields of research.

▪ **Recommendations:**

The team deserves as much support as possible to help it maintain its exciting research program whilst providing innovative imaging opportunities to the Pasteur community.



Team

Membrane Traffic and Pathogenesis

Name of team leader: Ms Chiara ZURZOLO

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2
N6: Other contractual staff (without research duties)	1	1
TOTAL N1 to N6	6	6

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	10	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	2



• Detailed assessments

Assessment of scientific quality and outputs

This unit has established itself at the front line of current research in the molecular cell biology of polarized epithelial cells and has successfully enlarged its activity to neurons with a focus on the mechanism of spreading of prions and other amyloid forming proteins. The group has investigated the role of glycosylation and of cholesterol in determining the apical sorting of GPI-anchored protein. On the neuronal side the group has shown that amyloid forming proteins can be transported from neuron to neurons via connecting nanotubes, but also via both anterograde and retrograde transport within the neuronal axon. Excellent papers have been published in high impact cell biology and biomedicine journals (e.g. J. Cell Science, Nature Cell Biol., Plos Pathogens, Mol. Biol. Cell, Biochem. J.).

Assessment of the team's academic reputation and appeal

The team leader is a highly regarded cell biologist and has been invited to write several reviews. She has been invited as speaker in the most important cell biology symposia.

The junior scientists in this group have begun to gain some visibility by being invited to present seminars in the EU. The unit research and fellowships are supported by several Pasteur Institute, French and EU grants.

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

The unit has collaborated and is collaborating with other groups of the Department.

The unit personnel is well distributed along the two lines of research, but a replacement of one personnel unit is still pending and the unit leader has convincingly argued for the need of an additional research position to be granted as soon as possible. The unit leader is highly motivated, and determined and appears to transmit her enthusiasm to the team members.

Assessment of the team's organisation and life

The plan for junior scientists to progress in their individual careers was presented and explained.

Members of the team were highlighted in the presentation and given the chance to present their own work.

Assessment of the team's involvement in training through research

A number of PhD and Master's students have been trained by this group and excellent papers have been generated by these individuals. The unit leader has organized a school in cell biology and has been invited to teach in several courses in and outside IP

Assessment of the strategy and the five-year plan

The primary project is the study of how prion and poly-Gln aggregates spread in different parts of the nervous system and how and where they become activated. A second line of research is focused around the study of the mechanism(s) of apical sorting of GPI-anchored protein in polarized epithelial cells.

Both lines of research are very relevant to the activity of a Department of Cell Biology and Infection and contribute to the other research lines present in the Department.



Conclusion:

- **Strengths and opportunities:**

The research plan is ambitious, but focused and promising.

- **Weaknesses and threats:**

The unit has the challenge of demonstrating the actual role of nanotubes in vivo, and of designing better assays of activation of prions and poly-Gln and of related toxicity in neurons.

- **Recommendations:**

The unit would benefit from the incorporation of a research scientist with experience in neuron biology/electrophysiology.



Team

Membrane Traffic and Cell Division

Name of team leader: Mr Arnaud ECHARD

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions		1
N3: Other permanent staff (without research duties)	0,2	0,2
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	5	5
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	6,2	7,2

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	2



• Detailed assessments

Assessment of scientific quality and outputs

The group of Mr Arnaud ECHARD addresses the membrane trafficking pathways that impact late steps of cytokinesis, with a particular focus on Rab35 and its interaction partners. The team leader has a strong background in cell biology, having trained at Curie and at UCSF university. Scientific quality and output of the group at Pasteur over the past 4 years has been outstanding, with three papers in top cell biological journals and several exciting stories in review.

In one important paper published in *Nature Cell Biology* (recommended by Faculty of 1000), the group showed an important interplay between Rab35 and Arf6 to control late cytokinetic endocytic events. Using TIRF microscopy and high resolution imaging, they demonstrated that when Arf6 is constitutively active, Rab35 is inactivated. This alters PIP2 levels, interferes with endocytic recycling and disrupts septin localization at intercellular bridges, causing cytokinesis to be defective. The work concisely demonstrated that an ARF/Rab GTPase cascade involving Rab35 and Arf6 is necessary for successful cytokinesis, opening up new areas of investigation related to GTPases' regulation of membrane traffic during cytokinesis.

In another standout *Nature Cell Biology* paper (recommended by Faculty of 1000), ECHARD's group found that Rab35 and its effector OCRL limit lipid and F-actin accumulation for successful cytokinesis abscission. The study was the first to show interaction between Rab35 and OCRL, which is the PI(4,5)P2 phosphatase mutated in Oculo-Cerebro-Renal Syndrome of Lowe's disease. They found that GTP-Rab35 binds OCRL through its ASH domain, with Rab35 depletion impairing the localization of OCRL to cytokinetic bridges. The phenotype was identical to that seen in Lowe's disease mutants of OCRL. Further data suggested that Rab35 recruits OCRL to the cytokinetic bridge where OCRL triggers actin disassembly, a necessary step for cytokinesis. They then showed that low doses of latrunculin (an actin disassembling agent) could reverse the cytokinetic defects occurring under Rab35 depletion or OCRL mutants. The results from this paper are highly significant, not only in showing the role of Rab35 in regulating actin disassembly during late cytokinesis but in demonstrating Rab35's relationship to OCRL. The findings represent a potential breakthrough in understanding how actin disassembly during cytokinesis is regulated through Rab35/OCRL crosstalk. Moreover, they suggest that Lowe syndrome represents an 'actinopathy' (i.e., defect in actin dynamics) potentially treatable by low doses of F-actin depolymerizing drugs. In addition to pointing to potential therapeutic applications, the work has stimulated collaborations between Mr Arnaud ECHARD's group and others at Pasteur in which the effects OCRL on F-actin modulation during phagocytosis of *Listeria* and in FcR uptake have been examined.

Assessment of the team's academic reputation and appeal

Overall, ECHARD's academic reputation is excellent and he is widely recognized in the field of membrane trafficking. His high status in the field of membrane traffic is evident from his numerous invitations to speak at international meetings (including ASCB, Japan Society of Cell Biology and Gordon Research Conferences). Moreover, ECHARD was elected Vice-President of the French Society for Cell Biology and has sought out excellent collaborators both at Institut Pasteur and internationally. The team has been successful at recruiting talented students and postdocs. The quality of Mr Arnaud ECHARD's team and his ability to provide mentorship was evident in an outstanding talk given by a junior member of the group.

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

Some of the findings from the team have translational implication for Lowe's disease and they have established collaborations with clinical colleagues to pursue this possibility. Their strategy of using low doses of latrunculin to treat Lowe's syndrome is original and could represent a breakthrough in treatment.

Assessment of the team's organisation and life

The organization and life of the team seems excellent. There has been a successful recruitment of talented students and postdocs and the team is organized in a coherent and logical manner with pooled resources available. The team employs cross-cutting scientific techniques that have led the group to interact with others at the Pasteur Institute. The team leader and his group seem collegial and are well liked at the Institute.



Assessment of the team's involvement in training through research

Mr Arnaud ECHARD can be ranked outstanding in terms of his involvement in training through research. In particular, he has been in charge of the 'Molecular Biology and the Physics of Biological Membrane' Master courses and is co-organizer of a "Cell Dynamics" course that recruits students from all over Paris. He is also a part-time Professor of Biology at the École Polytechnique, Palaiseau, France. In addition to being engaged in teaching in a variety of courses at Paris Universities and Pasteur Institute, he has served on a large number of thesis committees and is successfully mentoring students.

Assessment of the strategy and the five-year plan

The five-year plan and strategy is extremely ambitious and covers several areas of basic cell biology, including Golgi trafficking, polarity, cell division and cell fate determination. One common thread is the role played by Rab35, which is an exciting new player in this field. Testing whether Rab35/OCRL interaction is functioning as the central module for controlling PI(4,5)P2 homeostasis in cells should be a high priority. Also exciting is the project related to the fate of cytokinetic membrane and its potential role in long-term cell signaling.

Conclusion

- **Strengths and opportunities:**

Overall, the group's evaluation is outstanding. Their productivity and impact on the field of membrane trafficking and cytokinesis has been first rate, with much future potential. The proposed work is original and builds on prior work. The team demonstrated capacity for adaptation and change in strategic direction makes the work likely to succeed.

- **Weaknesses and threats:**

Although there was excitement about the various possibilities envisaged, there was also concern that the group might become too diffuse in trying to pursue so many areas of biology simultaneously.

- **Recommendations:**

The recommendation would be to focus efforts where the most novel and broad findings can be realized and to not try to do everything.



Team Platform Dynamic Imaging

Name of team leader: Mr Spencer SHORTE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)	8	8
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)	5	5
TOTAL N1 to N6	16	16

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended		
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		



• Detailed assessments

Assessment of scientific quality and outputs

The evaluated unit is an imaging platform and as such not a typical academic or research unit. The assessment is made with this fact in mind. The unit was not accessed in its capacity as a core facility. This unit, as an imaging platform, is very much the exception internationally in that a significant research portfolio is carried out. The unit has an interesting array of research and development projects. Many of them are carried out in a collaborative fashion. The projects are very interesting and cover probe development, development of instrumentation and software development. Appropriate for a core facility some of the projects have an incremental character since they are based on improving the functionality of the methodologies that are available to the users of the facility. A good example of this type would be the project supported by the Wellcome Trust to adapt the OMERa microscopy image database methodology, of the Swedlow group in Dundee, to the high content screening approaches that are very much of interest to the research community.

The unit produced a significant list of publications (e.g. PNAS, J. Microsc., Methods Enzymology). Amongst those, the paper in PNAS should be pointed out on the excitation of quantum dots (QDs) by bioluminescence that is both interesting scientifically and for the use of bioluminescence in small animal imaging. It relies on an excitation mechanism that is not based on energy transfer and allows, through the use of QDs an emission red shift that avoids many of the problems inherent in 'standard' bioluminescence imaging.

Assessment of the team's academic reputation and appeal

The leader has an excellent reputation in the field amongst developers of microscopy technologies.

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

The unit is involved in a significant number of international and national activities, which is one of the strengths of the unit. There are also significant interactions with companies. It also participates in an association of facility managers; next year an international meeting will be organized in Paris.

Assessment of the strategy and the five-year plan

The proposed projects are again often carried in collaborations and many are aimed at improving the technologies available for the users. Rather than relying on standard commercial systems this unit therefore can provide techniques that are not accessible to users of core facilities that only employ commercial systems. This significantly increases the type of experiments that the researchers at the Pasteur Institute and beyond can carry out, who are not themselves, developers of imaging technologies. An additional project is the Labex project where this unit will be part of a larger team to characterize the immune system of 1000 healthy individuals. A subset of 300 individuals will be analyzed using skin biopsies. This project hopes to obtain an understanding of the variability inherent in cell samples from healthy individuals, thereby providing a reference frame for high throughput screening studies of, for example, drug compounds.



Conclusion

- **Strengths and opportunities:**

In summary, as a platform unit, this unit conducts research at a very high level internationally. In fact this unit could serve as a model to other platforms, by illustrating the major benefits for the community that is served by a platform if a platform engages in high quality research.

- **Recommendations:**

It is very much appropriate for the research portfolio of a platform to have more of a development character than would be advisable for a basic research unit. This unit shows that very interesting work can be carried out in this context, by leveraging on research projects with commercial partners on the one hand, and the user community on the other hand.



5 • Conduct of the visit

Start: Monday December 2nd 2014, 8.30 a.m.

End: Tuesday December 3rd 2014, 6.00 p.m.

Visit site: Institut Pasteur

Institution: Institut Pasteur

Address: 25 rue du Dr. Roux, 75015 Paris

Programme of visit:

Monday December 2 ^{cd}	
Auditorium François Jacob Introduction: AERES coordinator / Mr Jean-Christophe OLIVO-MARIN/ Institut Pasteur representative 08.30 - 09.30 am	
Auditorium François Jacob	Room BIME 28-01-01 A
Committee 1 Mr Guy CORNELIS Mr Jonathan HOWARD Ms Jennifer LIPPINCOTT-SCHWARTZ Mr Raimund OBER Ms Ana POMBO Mr Alain CHARBIT (INSERM) Mr Didier LERECLUS (INRA)	Committee 2 Mr Pier Paolo DI FIORE Mr Roberto MAYOR Mr Cesare MONTECUCCO Mr Jacques NEEFJES Mr Moshe OREN Mr David SIBLEY Ms Claire FRANCASTEL (INSERM) Mr Paul MANGEAT (CNRS)
Unit of Mr Jean-Christophe OLIVO-MARIN 09.30 - 11.00 am	Unit of Ms Alice DAUTRY-VARSAT 09.30 - 10.45 am
Coffee-Break. Exchange Ms Jennifer LIPPINCOTT-SCHWARTZ & Mr Jacques NEEFJES	
Unit of Mr Christophe ZIMMER 11.30 - 12.45 pm	Unit of Ms Chiara ZURZOLO 11.15 - 12.45 pm
Lunch 12.45 - 02.15 pm	
Auditorium François Jacob	Room 28-01-01 A, F. Jacob bldg
Unit of Mr Jost ENNINGA	Unit of Ms Sandrine ETIENNE-MANNEVILLE 02.15 - 03.45 pm



02.15 - 03.45 pm	
Coffee-Break	
Imagopole Platform of Spencer Shorte 04.15 - 05.15 pm	G5 of Mr Arnaud ECHARD 04.15 - 05.15 pm
3 parallel meetings with research staff, technical staff, graduate students/postdocs 05.15 - 06.15 pm	
Tuesday December 3rd	
<p>Committee 1</p> <p>Mr Guy CORNELIS Mr Richard MOXON Mr Jonathan HOWARD Mr Cesare MONTECUCCO Mr Jacques NEEFJES Mr Raimund OBER Mr Alain CHARBIT (INSERM) Mr Didier LERECLUS (INRA)</p>	<p>Committee 2</p> <p>Mr Pier Paolo DI FIORE Ms Jennifer LIPPINCOTT-SCHWARTZ Mr Roberto MAYOR Mr Moshe OREN Ms Ana POMBO Mr David SIBLEY Ms Claire FRANCASTEL (INSERM) Mr Paul MANGEAT (CNRS)</p>
Auditorium François Jacob	Room 14-15, Lwoff bldg
Committee 1	Committee 2
Unit of Ms Pascale COSSART 09.00 - 10.45 am	Unit of Mr Alain ISRAEL 09.00 - 10.45 am
Coffee-Break	
Unit of Mr Philippe SANSONETTI 11.15 - 01.00 pm	Unit of Ms Anne DEJEAN 11.15 - 01.00 pm
Lunch with representatives of supportive institutions Pasteur Institute, CNRS and INSERM 01.00-02.30 pm	
Room 14-15, Lwoff bldg : Expert Committee Meeting 02.30-06.00 pm	



6 • Supervising bodies' general comments

Alain Israël

Le 19 mars 2014

Directeur de l'Evaluation scientifique



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AERES report on Dept of Cell Biology and Infection

Comments on the review of the Imaging core facility (pages 46-48 of the AERES report) :

Inasmuch as the PFMU did not originate, or conduct any independent research activity its work was considered outside the scope of the formal AERES review and therefore not included in the final report. The department BCI would, however, like to acknowledge the efforts, expertise and services rendered by the PFMU team members led by Marie-Christine Prevost during the last five years, and recognize the quality of the PFMU facility and the added value it has brought to the research community at large.

Spencer Shorte & Jean-Christophe Olivo-Marin

Alain Israël
Directeur de l'Evaluation scientifique