CIMI - Centre d'immunologie et de maladies infectieuses

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Centre d'Immunologie et des Maladies Infectieuses

CIMI

Under the supervision of the following institutions and research bodies:

Université Paris 6 - Pierre et Marie Curie

Centre National de la Recherche Scientifique

Institut National de la Santé et de la Recherche Médicale

February 2013

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

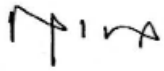
Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head



Pierre Glaudes

The president of AERES "signs[...], the evaluation reports, [...]countersigned for each evaluation department by the relevant head of department (Article 9, paragraph 3, of french decree n°2006-1334 dated 3 november 2006, revised).

Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).
This score (A+, A, B, C) concerned each of the six criteria defined by the AERES.
NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

Criterion 1 - C1 : Scientific outputs and quality ;
Criterion 2 - C2 : Academic reputation and appeal ;
Criterion 3 - C3 : Interactions with the social, economic and cultural environment ;
Criterion 4 - C4 : Organisation and life of the institution (or of the team) ;
Criterion 5 - C5 : Involvement in training through research ;
Criterion 6 - C6 : Strategy and five-year plan.

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

- Grading table of the unit: Centre d'Immunologie et des Maladies Infectieuses

C1	C2	C3	C4	C5	C6
A+	A	A	A	A+	A+

- Grading table of the team: Strategies in Vaccination and Immunity (SVI)

C1	C2	C3	C4	C5	C6
A	A	A	NN	A	A

- Grading table of the team: Cellular and Molecular Immunology of Chronic Inflammatory Diseases (ICID)

C1	C2	C3	C4	C5	C6
A	A	A	NN	A	A

- Grading table of the team: Immunobiology of Viral Infections and Antigen Presentation

C1	C2	C3	C4	C5	C6
NN	NN	A	NN	A	A

- Grading table of the team: Persistent Viral Infections

C1	C2	C3	C4	C5	C6
A	A	A	NN	A+	A

● Grading table of the team: Emergence and Diffusion of Multiple Bacterial Resistance against Antibiotics

C1	C2	C3	C4	C5	C6
NN	NN	A	NN	B	A

● Grading table of the team: Immune-intervention and Biotherapy

C1	C2	C3	C4	C5	C6
NN	NN	A	NN	NN	A

● Grading table of the team: Treg Biology and Therapy

C1	C2	C3	C4	C5	C6
A+	A	A	NN	A	A+

● Grading table of the team: Erythrocytes, Parasites and Pathogenesis

C1	C2	C3	C4	C5	C6
NN	NN	A	NN	A	A+

● Grading table of the team: NK and Pathologies

C1	C2	C3	C4	C5	C6
NN	NN	A+	NN	A	A+

● Grading table of the team: Pathogenesis of Viral Infections and Immune Aging

C1	C2	C3	C4	C5	C6
A+	A	A	NN	A+	A+

● Grading table of the team: Chemokines in the Process of Inflammation

C1	C2	C3	C4	C5	C6
A+	A	A	NN	A+	A+

- Grading table of the team: Identification and Pre-Clinical Validation of Novel Targets against Malaria

C1	C2	C3	C4	C5	C6
A+	A	A	NN	A+	A+

- Grading table of the team: Immunity and Immunogenetics against Viruses and Vaccines (I2V2)

C1	C2	C3	C4	C5	C6
A	A+	A+	NN	A+	A+

- Grading table of the team: Molecular Biology and Immunology of Malaria Liver Infection

C1	C2	C3	C4	C5	C6
NN	NN	NN	NN	NN	A+

Evaluation report

Unit name:	Centre d'Immunologie et des Maladies Infectieuses
Unit acronym:	CIMI
Label requested:	UMR
Present no.:	
Name of Director (2012-2013):	
Name of Project Leader (2014-2018):	Mr Christophe COMBADIERE

Expert committee members

Chair:	Mr Camille LOCHT, Institut Pasteur, Lille
Experts:	Mr Jean-Marc BALLOUL, Transgene, Illkirch-Graffenstaden
	Mr Monsef BENKIRANE, University of Montpellier
	Ms Véronique BRAUD, University of Nice
	Mr Volker HEUSSLER, University of Bern, Switzerland
	Mr Jacques IZOPET, University of Toulouse
	Ms Valérie JULIA, University of Nice (INSERM representative)
	Ms Jacqueline MARVEL, University of Lyon
	Mr Olivier NEYROLLES, IPBS Toulouse (CoNRS representative)
	Mr. Michel SIMONET, University of Lille (CNU representative)
	Mr Tim SPARWASSER, Hannover Medical School, Germany
	Mr Andy WATERS, University of Glasgow, United Kingdom

Scientific delegate representing the AERES:

Mr Joost Van MEERWIJK

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

Mr Paul INDELICATO, Pierre and Marie Curie University

Ms Evelyne JOUVIN-MARCHE, CNRS

Ms Bernadette MURGUE, INSERM

1 • Introduction

History and geographical location of the unit

Creation of a research center located at the Pitié-Salpétrière Medical School and at the CERVI Building

- Faculté de Médecine, 91 boulevard de l'Hôpital,5th and 6th floor, 75013 Paris
- Cervi Building , 83 Boulevard de l'hôpital, 3rd and 4th floor, 75013 Paris

The groups joining this new research centre are currently in the "Institut Fédératif de Recherche 113" at the Pitié-Salpétrière site.

Management team

This new Research Centre will be headed by Dr. Christophe Combadière. He will be assisted by an executive committee consisting of six of the 14 group-leaders, representing all four global themes addressed by the CIMI. All team leaders as well as one representative of the technicians, the postdoc/PhD-students, and the other permanent staff each will form the CIMI Scientific board. Finally, a scientific advisory board, consisting of six external French and foreign specialists, will provide help on strategic decisions.

AERES nomenclature

SVE1_LS6 Immunology, microbiology, virology, parasitology.

Unit workforce

Unit workforce	**Number as at 30/06/2012**	**Number as at 01/01/2014**	2014-2018 **Number of project producers**
N1: Permanent professors and similar positions	38	44	39
N2: Permanent researchers from Institutions and similar positions	18	22	22
N3: Other permanent staff (without research duties)	23	25	24
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	1	1
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	27	33	26
N6: Other contractual staff (without research duties)	19	20	14
TOTAL N1 to N6	**126**	**145**	**126**

Percentage of producers	***100%***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	37	
Theses defended	44	
Postdoctoral students having spent at least 12 months in the unit*	25	
Number of Research Supervisor Qualifications (HDR) taken	14	
Qualified research supervisors (with an HDR) or similar positions	38	43

2 • Assessment of the unit

Strengths and opportunities

Some of the teams have made substantial contributions to their field and have a very strong publication record (papers were published in N. Engl. J. Med., Nat. Med., Immunity, etc.). Some of the key scientists have a very strong international recognition.

There is a very strong emphasis on translational research, including clinical trials, and some of the work has already led to novel therapeutic attitudes.

There is a very good integration of almost all the teams within the CIMI, with many collaborations among teams within the CIMI.

Many patents have been applied for, and there is good interaction with industry, including the emergence of start-up companies.

There is very good access to human samples, and a good integration of human studies and animal models.

The presence of three national reference centres is an important asset, and these are well integrated into the CIMI project.

There is a good training program of PhD students and postdoctoral fellows, including a "Club" of free exchange of information and discussion between all PhD students and postdoctoral fellows of the CIMI.

The choice of the Director for the CIMI is very good.

There has so far been an impressive amount of external funding.

Weaknesses and threats

Not all of the teams have published in high impact journals. Some of the teams remain modest in the choice of their journals, although their research has a great potential. Not all of the teams have a strong international visibility, for some it remains rather local.

There is no ERC grant, and coordination of FP7 programs is not frequent (although not inexistent).

Not all teams are equally strongly involved in translational research. Some have very little interaction with industry, and have no patent applied for.

It is not clear how laboratory space and technical support is allocated to the different teams.

The SAB is not sufficiently international.

The executive committee is only composed of 6 of the 14 team leaders.

There is not sufficient laboratory space for some of the teams.

The CIMI is spread over several buildings.

There is a lack of administrative staff.

No deputy director has been chosen.

There are no plans for the recruitment of new, external teams.

Recommendations

Some of the teams should try to publish in higher impact journals and strengthen their international visibility by participating in international networks, programs, and other events.

There should be a collective effort to apply for ERC grants and other EU projects.

There should be a clear strategy on how laboratory space and technical support is allocated to the different teams.

The SAB should be made more international.

The executive committee should include all 14 team leaders to take the essential decisions.

Administrative staff should be increased. This will be important especially if the CIMI will be a Centre of three institutions (University, CNRS, INSERM).

It is essential to elect a deputy director (not a "co-director"), because the workload will be too heavy for a single director.

It is essential that the CIMI strongly considers the recruitment of new, external teams. This is very important for its future development.

3 • Detailed assessments

Assessment of scientific quality and outputs

The CIMI project is a new application for a Research Centre on Immunology and Infectious Diseases. For the most part, the 14 teams come from an "Institut Fédératif de Recherche" (IFR113, named "Immunity, Cancer and Infection"). This IFR has produced roughly 500 papers between 2007 and 2012, of which 47 were signed by the members of the CIMI project as first or last author. Several of these papers were published in high impact journals (IF > 9), such as N. Engl. J. Med. (1 paper), Nat. Med. (1 paper), Immunity (3 papers), J. Clin. Oncol. (2), J. Clin. Invest. (4), Circulation (2), Host Cell Microb. (1), J. Exp. Med. (3), Am. J. Respir. Crit. Care Med. (2). However, the level of publications is rather heterogeneous between the teams. Nevertheless, all teams have published in good international journals. Some teams have only published in speciality journals of their discipline. Several important scientific results have been obtained by members of the CIMI project. Some of them have led to novel therapeutic approaches, some have an impact on national treatment policies. Novel avenues and original approaches have been explored, both in basic and applied aspects (including new vaccine administrations) of the research. There is an excellent focus of all groups on translational research.

Assessment of the unit's academic reputation and appeal

Members of the IFR113 have organized or co-organized national and international meetings, mostly in immunopathology (e. g. AIDS, auto-immunity) and immunotherapy (including vaccinology). Several senior scientists are regularly invited to international conferences, as speakers or chairpersons. These meetings include Keystone symposia, Gordon Research Conferences. One of the group leaders is considered among the top 1% in his field at a global level.

Members of the CIMI project are also editors of scientific journals, including the official journal of the international AIDS society (AIDS, IF 6.2).

Some teams participate or coordinate international research programs, some coordinate national programs and networks. There are three National Research Centres in the CIMI project (Malaria, tuberculosis, and lupus erythematous). Institutional prizes have been awarded to several CNRS and Inserm scientists (mainly team leaders) for research excellence. Three Inserm scientists were recruited over the past five years.

However, there is also important heterogeneity among the teams. Some teams have only limited visibility, essentially at the national level and are not aggressive enough in their participation in international conferences and events. There is no ERC grant, and participations in FP7 programs are not many, although some do exist.

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

One of the important assets of the CIMI project is the strong involvement of all teams in translational research. There is a clear aim at bringing results generated from basic research to clinical applications.

19 patent applications have been deposited, and many of the team members have close interactions with the pharmaceutical industry. Many contracts have been established between CIMI teams and industrial partners. In addition, over the last five years, three teams have initiated start-up biotech companies.

The CIMI teams have developed active dissemination plans of scientific knowledge, including radio and TV broadcasting and open days for various patient's associations, in particular for AIDS patients.

Some of the work done by CIMI teams has an important impact on therapeutic attitudes and preventive strategies, including vaccines.

However, important disparities exist here as well among the teams with some of them heavily involved in patenting, industrials contracts and communication to the public on national and international levels, and others are too poorly involved in valorisation and communication activities.

Assessment of the unit's organisation and life

The CIMI council is appropriate, in particular postdocs, students, technicians etc. are associated to the CIMI council. The creation of the "career evolution" committee to assist students and staff leaving the unit is an excellent initiative.

There is a very good integration of all the teams in the overall project. All try to collaborate with each other, even though they are in different buildings. A good system is in place for optimal use of platforms, and the three national reference centres are very well integrated. All teams have a strong focus on translational research, and the existence of a Clinical Investigation Centre is an important aspect. The choice of the director for the first term (elected democratically) is excellent.

However, the SAB is not sufficiently international. The executive committee is composed of only six team leaders; it would be better if all 14 were involved. Also, there is no deputy director, which may be a problem (overload of work for the Director), and the administrative staff is too limited, as well as the technical support staff (e. g. dish washing etc.).

It is also not clear how lab space and technical staff is allocated to the different teams. This is especially critical, as lab space is very limited for some of the teams. Finally, there are difficulties to recruit new teams. No plan for the recruitment of new teams exists. This is explained by the lack of lab space, but it is essential that a research centre has the capacity to welcome new teams.

Assessment of the unit's involvement in training through research

With a total of 17 professors and 27 permanent assistant professors (with or without medical duties), the CIMI is strongly involved in outstanding teaching in immunology and microbiology. 95 and 70 students were involved in a PhD project and a Research Master, respectively.

Several international education programs (of which the international Master program "immunotechnologies and biotherapies") are directed or co-directed by members of the CIMI. In addition, an average of 18 seminars/year by outstanding international guest speakers, open to PhD students, have been organized

Currently, the CIMI comprises over 30 PhD students and approximately the same number of postdoctoral fellows. However, they are not homogeneously distributed among the teams, some teams have very few if any postdoctoral fellows (despite the size of the team).

The career of graduated PhD-students and postdocs leaving the unit is often difficult to appreciate and was not always well described.

Assessment of the five-year plan and strategy

There are clear efforts to make the research very integrative among the CIMI members, with three clear research programs, each involving several teams. All 14 CIMI teams are strongly involved in translational research, essentially in innovative vaccination and anti-inflammatory therapeutic strategies. This is really a hallmark of the CIMI. There is already a good amount of collaborations between teams within the CIMI, although some of the teams still lack full integration and appear to be only loosely associated with other teams.

The three innovative research programs developed, upon recommendation by the Scientific Advisory Board, are (i) development of novel vaccines and biotherapies, (ii) analysis of host-pathogen interactions (concerning agents causing major public health concerns, essentially HIV, *Plasmodium*, hepatitis viruses, and *Mycobacterium*), and (iii) investigations of innate and adaptive immune responses as well as inflammatory responses during infectious and auto-immune diseases.

The CIMI has access to state-of-the-art facilities to develop its research program and it has demonstrated during the past years its capacity to raise substantial funding.

There is also a strong commitment to become a national reference centre in immunology and infectiology.

Finally, there are a number of emerging teams with young team leaders that have come out of previously existing groups, there is thus a demonstrated good capacity to give the chance to young teams and team leaders.

4 • Team-by-team analysis

Team 1 : Persistent viral infections

Name of team leader: Mr Henri AGUT

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	8	8	8
N2: Permanent EPST or EPIC researchers and similar positions	1	1	1
N3: Other permanent staff (without research duties)	4	4	4
N4: Other professors (PREM, ECC, etc.)	1	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2	2
N6: Other contractual staff (without research duties)	4	4	4
TOTAL N1 to N6	**20**	**19**	**19**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	13	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	9	9

• Detailed assessments

Assessment of scientific quality and outputs

The team is the merger of 3 research groups located in distinct centres:

- IFR113 – Pitié Salpétrière – EA2387 then ER1 UPMC "Dynamics, Epidemiology and Treatment of Viral infections".

- Centre des Cordeliers – Eq 6, UMR 5872 INSERM « Alarmins and viral persistent infections ».

- Centre Necker – INSERM U845 « Pathogenesis of HBV-related viral hepatitis ».

The PI's group covered a broad spectrum of scientific goals (diagnosis, epidemiology and resistance to antivirals) as well as different viruses inducing long-term chronic infections (HIV, HBV, HCV and human herpesviruses). In 2009, the research group on HIV resistance left the team.

The main questions addressed were the pathogenic role of chromosomally integrated human herpesvirus 6 (ciHHV6) and the pathophysiology of chronic HBV infections.

Overall, the team has published 55 articles (hepatitis viruses and herpesviruses) in respected speciality journals, e.g. J Infect Dis (5), PLoS Pathog (1), Am J Respir Crit Care Med (1), J Clin Virol (8), Antiviral Therapy, J Clin Microbiol and Antiviral Research.

The second group has focused its research on the contribution of HMGB1 (High Mobility Group B1) in viral infections. They demonstrated that intracellular HMGB1 contributes to EBV genome maintenance (J Virol 2012) and that extracellular HMGB1 acts both as a stress signal and as a modulator of viral infections (AIDS 2007; J Immunol 2011). They also demonstrated the existence of autoantibodies to HMGB1. The group has published 23 articles.

The third group is well known in the field of pathogenesis of HBV infection. It has investigated the direct role of HBx and HBSP proteins in liver fibrogenesis and carcinogenesis. It has also developed a humanized mouse model susceptible to infection by hepatotropic pathogens including HBV. The team has published 23 articles from 2007 to 2012, among which 11 with an author from the group in key position (either first or last author).

As a whole, this team therefore has a good scientific quality and output.

Assessment of the unit's academic reputation and appeal

Several investigators of the team are invited to communicate in international events (International Conference on HHV6 and HHV7) and a team member directed a European network (Herpesviruses and cancer). The academic reputation of this team is therefore very good.

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

Numerous contracts with diagnosis and pharmaceutical companies have been obtained. A strong expertise in safety of health products must be underlined. The team leader participated to many radio and TV broadcasts on viruses. The team's interaction with the social and economic environment is therefore excellent.

Assessment of the unit's organisation and life

The structure of the team is recent. Despite a real will to optimize synergies between researchers of the team, the lack of common working surfaces could be an obstacle.

Assessment of the unit's involvement in training through research

There is a strong involvement in research training. A total of 13 PhD theses were defended and 3 postdoctoral fellows were trained. A professor is Chief supervisor of the Master degree in Microbiology and Chief supervisor for 3 masters sections.

Assessment of the five-year plan and strategy

The project has two major axes: (i) studying microenvironmental factors and pathophysiology of persistent viral infections with three virus models (EBV, HHV6, and HBV) and (ii) establishing therapeutic strategies against persistent viral infections (viral inhibitors alone or combined with cell function modulators).

All the projects are scientifically and clinically relevant:

- contribution of HMGB1 to EBV-related cancers in HIV patients.

- impact of defective viruses and viral proteins (HBx, HBSP, HBs) on HBV pathogenesis.

- significance of chromosomal integration of HHV6 during pregnancy and hematopoietic stem cell transplantation.

The research program is well focused and based on several tools (including animal models) that were developed in the previous period. Several links between the topics (alarmins, antivirals) should provide the cohesion of this new team.

However, the diversity in the program may also be a handicap for publications in high impact journals.

Conclusion

● Strengths and opportunities:

Several collaborations already established with other CIMI teams should be reinforced for consolidating the research program and benefiting of a number of opportunities. The team has a good expertise in persistent viral infections.

● Weaknesses and threats:

The lack of common working surfaces could induce difficulties for obtaining a real synergy between the different groups of the team. The low number of full-time researchers could slow down the development of new concepts or approaches in the very competitive field of cancer research.

● Recommendations:

The team should remain focused on the models of persistent viral infections with the highest potential for novelty.

Team 2 : Immunopathogenesis of viral infections and immune aging

Name of team leader: Mr Victor APPAY

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	0	2	
N2: Permanent EPST or EPIC researchers and similar positions	2	2	2
N3: Other permanent staff (without research duties)	1	1	1
N4: Other professors (PREM, ECC, etc.)	0	0	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	4	2
N6: Other contractual staff (without research duties)	2	2	2
TOTAL N1 to N6	**7**	**11**	**7**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2	1
Theses defended	1	3
Postdoctoral students having spent at least 12 months in the unit	1	3
Number of Research Supervisor Qualifications (HDR) taken	1	2
Qualified research supervisors (with an HDR) or similar positions	1	2

• Detailed assessments

Assessment of scientific quality and outputs

The team focuses on CD8+ T cells in the control of HIV infection and on immune aging by chronic HIV infection. Polyfunctionality and antigen sensitivity of HIV-specific CD8+ T cell clones have been studied. Public "clonotypes" were identified that are shared between different individuals and found to have high antigen sensitivity. The observations of the team question PD-1 as a marker of T cell exhaustion. They found that the inability to produce new T cells is a major factor for the progression to AIDS, that the loss of CD4+ T cells is associated with a general exhaustion of lymphopoiesis, that this damage can persist in spite of successful anti-viral treatments.

These are major contributions in the field for a relatively small group. This qualifies the production of the team as truly excellent. However, the mechanistic aspects of the project are not yet sufficiently approached. The work has been published in high-ranking journals, including J. Exp. Med., Nat. Med., Blood, J. Clin, Invest., a total of 21 articles published over the last 5 years, mostly with team members as the principle authors (first or last). Overall this activity is thus judged to be excellent.

Assessment of the unit's academic reputation and appeal

The team has many national and international collaborations, has secured important national funding (no international funding). The team leader has been awarded the Inserm excellence award, has been invited to many national and international meetings and was ranked within the top 1% scientists.

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

The team leader has a "Contrat d'interface" as expert for the Paris hospitals, is a member of two working groups and has organized several international workshops. He is also member of several national advisory boards. There is relatively little interaction with industry, no patent application.

Assessment of the unit's organisation and life

The group is composed of two senior scientists (2 FTE), both with a good publication record, 1½ FTE technician/engineer, one post-doc and two PhD students. All seem to be well integrated in the team, and there are several common publications.

Assessment of the unit's involvement in training through research

The team leader teaches 10-15h per year (Master in Immunology, biology of aging), has trained three post-docs, three PhD students and three Master students. Finally, the team leader is a lecturer in a European course in clinical cytometry and at the French Society of Immunology. Given the relatively small size of the team, this training through research activity is thus judged to be excellent.

Assessment of the five-year plan and strategy

There is a plan for a university Professor to join the team. The main themes of the team will be similar to the previous ones, and the project is built on solid data obtained by the group. The project will contain a strong translational aspect. The focus of the research will increasingly be immune aging. The hypothesis is that chronic viral infection-induced recurrent inflammation causes immune exhaustion and defects in lymphopoiesis. The project is highly original and has good feasibility. The findings will be of the utmost importance for future immuno-interventions in the elderly or chronically infected individuals. However, the mechanistic aspects are not sufficiently pursued.

Conclusion

● Strengths and opportunities:

The science developed by the team is cutting edge, with a strong potential of high impact. The team has made major contribution to the field and published in high impact journals as principal author (including J. Exp. Med., Nat. Med., Blood, J. Clin, Invest). As such, the team head is ranked within the top 1% in its research area.

The team has also secured important funding and it has many national and international collaborations, which largely contributes to its international visibility.

● Weaknesses and threats:

There is relatively little interaction with industry, the team has not applied for patents. Moreover, the research has remained rather observational for the most part, and the mechanistic aspects of the scientific observations at the molecular and cellular levels are not yet sufficiently developed.

● Recommendations:

The committee recommends the team to remain well focused on the most interesting aspects of the project (which is actually the case). The team should better develop mechanistic aspects and try to have industry interested in the project.

Team 3 : Immunity and immunogenetics against viruses and vaccines

Name of team leader: Ms Brigitte AUTRAN

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	4	5	5
N2: Permanent EPST or EPIC researchers and similar positions	2	3	3
N3: Other permanent staff (without research duties)	1	3	3
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)			
N6: Other contractual staff (without research duties)	0.5	0.5	0.5
TOTAL N1 to N6	**7.5**	**11.5**	**11.5**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	3	4

• Detailed assessments

Assessment of scientific quality and outputs

This team is strongly involved in translational research. It works essentially on immunity and vaccination to viral infections. In particular, the team has made substantial contributions to different aspects of HIV infection. The immune control of the HIV reservoir was studied in a large cohort of non-progressors, especially their genetic polymorphism. This has evolved into one of the major themes of the team. In addition, studies on the genetic susceptibility to HCV have been conducted. Another important theme concerns HIV vaccine research, in particular on therapeutic vaccine mechanisms. Immunity to influenza vaccines, in particular in immuno-suppressed groups, has also been studied. Finally, the immune control of oncoviruses in HIV patients has been studied, in particular HHV-8 involved in Karposi sarcoma.

The team has published over 170 manuscripts within the evaluation period. All the PIs within the team have published as senior last author. The team leader has published 26 manuscripts as senior last author. Despite this quantitatively very good scientific production, most of the manuscripts were published in specialised journals such as Blood, AIDS, CID, J. Immunol, Vaccin, Immunogenetics etc.

Assessment of the unit's academic reputation and appeal

The team is internationally recognized in the field of infection/immunity and vaccine. The team leader often acts as Co-chair of international meetings (e.g. Keystone, AIDS Vaccine), as a member of scientific organizing committees (European congress of immunology, AIDS vaccine, IAS, etc.) and as an invited speaker to international meeting (CROI, AIDS vaccine, IAS etc.). The team leader is often invited to write reviews in high impact journals (Lancet, Science, Nature Medicine, etc.). She acts as Editor of AIDS. She was the co-director of the IFR113 (Immunité-cancer-Infection). The team is involved or has been involved in an EU project (EU-FP7 Cuthivac consortium) and developed international and national collaborations with top laboratories in the field of viral persistence, vaccine and immune response against HIV and other viruses. The team also hosts well-established world leaders and talented postdocs from abroad. It therefore has an excellent academic reputation.

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

The team leader has been and is currently involved in decision making at the political level whenever vaccine strategies are to be discussed both at national and EU levels, which attests of an excellent interaction of the team with its environment.

Assessment of the unit's organisation and life

N/A

Assessment of the unit's involvement in training through research

Members of the team are heavily involved in national educational program at the national level. The team members have trained 11 PhD students and 8 master students. PhD students participate in international meetings where they are often selected for oral presentation. They often complete their degree within 3 years and are usually first authors on the teams' publications. The team has an excellent reputation for training PhD students since they often join excellent laboratories for their postdocs. The team organizes many external seminars with outstanding speakers.

Assessment of the five-year plan and strategy

The team is well structured around three major complementary aims. These concern the immune control of HIV reservoirs and the potential immune interventions, T cell responses to oncogenic viruses (HHV-8, EBV, HPV and HCV) in the context of immune suppression, and GWAS on chronic viral infections, essentially HIV and HCV. The PIs in charge of each project have excellent experience in their respective fields. The projects are well structured and the team has all the tools and techniques in house that ensure the success of the project. The projects are ambitious and highly competitive. Although the projects are excellent, timely and, if successful, will make an outstanding contribution to the field, they lack some specificity and mechanistic insight. The project will greatly benefit from the recruitment of talented post docs or researchers who can take the aims one step further toward mechanistic understanding (basic mechanisms of the cell determinants involved in the establishment of the viral reservoir, the role of the identified genetic determinant to understand the susceptibility to HIV/AIDS and towards the interaction between HIV and oncoviruses).

Conclusion

- Strengths and opportunities:

The team has an excellent international reputation and has really made substantial contributions in the field of HIV immunity, vaccine research and other chronic or oncogenic viruses. The research is very strongly translational, almost exclusively in the human model. The impact of the research is very strong, both for vaccine development and for public health. The publication record is very strong, and all the PIs of the team have published.

The team leader is very active in international meetings and working group, and is certainly an authority in the field. There is an excellent connection with the European and international community.

Funding has been very good, and contacts with industry are many. The team is also involved in decision making bodies, both at the national and European levels.

- Weaknesses and threats:

The whole field appears to be a bit stuck with respect to vaccination against HIV, and there is no guarantee that in the future these problems will be solved.

Although the team has been very active in publishing, most articles were published in specialized journals, rather few in high-impact journals of general interest.

The project is well structured, but appears very ambitious, which may be a threat for maintaining the international leadership of the team in its main themes.

- Recommendations:

It is recommended that the team keeps on going with the good work. The project looks very interesting with a strong potential for important findings. However, the team should take care in avoiding broadening too much its research themes. This might result in un-focussing and thereby loss of competitiveness.

An effort should be made to try and publish in high-impact general journals. Some of the projects most certainly will yield results that may be published in such journals.

The recruitment of a talented post-doc with his own ideas on how to tackle the problems encountered would be an important asset.

Team 4 : Parasites Erythrocytes Pathogenesis

Name of team leader: Mr Pierre BUFFET

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2	2	2
N2: Permanent EPST or EPIC researchers and similar positions	0	0 or 1	0 or 1
N3: Other permanent staff (without research duties)	0	0	0
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	3	3
N6: Other contractual staff (without research duties)	0	0	0
TOTAL N1 to N6	**4**	**5 or 6**	**5 or 6**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	2
Theses defended	0	1
Postdoctoral students having spent at least 12 months in the unit	2	2
Number of Research Supervisor Qualifications (HDR) taken	0	0 or 1
Qualified research supervisors (with an HDR) or similar positions	1	1 or 2

• Detailed assessments

Assessment of scientific quality and outputs

The team aims at investigating the clearance of *P. falciparum*-infected red blood cells in the human spleen and how the parasite tries to avoid clearance. The role of the spleen in malaria was underestimated for a long time and the work of this team helped a lot to shed some light on this aspect.

This is original research that has generated approaches to the examination of important features of malaria pathophysiology that are novel and unique. The team has generated data that is published in high quality journals. Production of these novel methodologies and demonstration of their effectiveness in examining the filtration effects of the spleen on parasitized human erythrocytes containing either asexually dividing or sexually developing *Plasmodium* parasites, are excellent.

Some of the work of the team has changed national policy with regard to treatment of imported malaria from quinine to artemisinine.

The PI of the team is considered to be a world leader in his area. He has already published work on isolated human spleens and their function in high ranking journals (several papers as last or first author in Blood) and it can be predicted that the work on pitting of artesunate-treated RBCs in spleen and the newly developed filter system will have a deep impact in the field. Thus, the data will be of interest for a very broad readership.

The performance of the PI so far was excellent, in particular considering that he has many other duties. He is very active on a national and international level and is expert for several aspects of parasitic diseases.

Assessment of the unit's academic reputation and appeal

The team is highly visible in the field, and the PI was invited as a keynote speaker to many conferences to present his work on isolated human spleens and the filtration of infected RBCs. He is coordinator of WHO recommendations for the treatment of leishmaniasis in the WHO EMRO (Eastern Mediterranean Region).

The PI of the team is head of the "In vitro surveillance module" of the Worldwide Antimalarial Resistance Network (WARN) and co-author of French Recommendations for the Treatment of Severe Malaria. He was invited to the closed-door meeting of the "Medicine for Malaria Venture" in Vienna.

The team has extensive national and international collaborations. It is accepting post-doctoral workers from collaborating labs for extensive periods of time and similarly sending team members to other laboratories.

Funding sources are diverse and the Bill & Melinda Gates foundation has invested in three years of funding in one project with another project also currently funded. CIFRE funding, indirect support, ARC (post doc), Fondation Follereau, and significant LabEx resources have also been obtained. Together, the funding of the project is extraordinary good and the project has a very good perspective.

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

The unit contributed to a number of patents (three patent-applications). Most relevant are the patents on drug screening using the filtration system. Whether this will have an economical impact is difficult to predict but it demonstrates the activity of the group and the PI in translational research. The PI is definitely a strategic leader in the field concerning the role of the spleen in clearance of blood stage *Plasmodium* parasites. International collaborators are well chosen and guarantee the access to artesunate-treated patients to further investigate the delayed anaemia in artesunate-treated patients.

The PI has also important implications in national policies on malaria treatment and has participated in national radio broadcasts.

Assessment of the unit's organisation and life

N/A

Assessment of the unit's involvement in training through research

Two PhD students have been trained, and the PI is involved in university teaching to undergraduates. The PI is MD and has many other duties. It is therefore difficult for him to fully concentrate on the project. This situation is far from optimal and delays the progress in a highly competitive field.

Assessment of the five-year plan and strategy

The project is cutting edge science in terms of the methodology used and the working hypothesis. It combines aspects of clinical and basic research and therefore fits perfectly in the CIMI philosophy. The goals are clearly defined and a very good schedule with milestones has been provided. The research project has two very closely related main axes: analysis of red blood cell (RBC) microcirculation in the spleen and analysis of parasite pitting in the spleen before and after artemisinin treatment. Little is known about the physiology of RBC circulation in the spleen. The discovery of a very innovative and clever filter system that closely resembles the filtration in the spleen is a major methodological breakthrough in the field of spleen research in general and malaria research in particular. With this newly revealed filter system it can now be investigated how infected red blood cells behave before and after treatment with drugs. This system can also be applied to screen for anti-malarial drugs. First results show that artemisinin-treated red blood cells are retained by the spleen filtration system and that the parasite is then removed from the RBC by pitting. This highly relevant and exciting observation will be further analysed and the phenomenon of delayed anaemia of artesunate-treated patients will be investigated. It is planned to further optimize the filtration system by employing microfluidic approaches for drug screening. Together, the five-year plan is very well thought through and there is a clear and straightforward strategy. However, manpower is the bottleneck of this project. Recruitment of a permanent scientist would be highly advisable. The PI confirmed that an additional postdoc has been hired and will start in the near future. This will definitely improve the personal situation but it does not replace a scientist position. This very well funded project may suffer important delay because of the lack of manpower.

Conclusion

- Strengths and opportunities:

The team presents a highly innovative cutting edge approach to an important problem in malaria pathophysiology, which has so far largely been overlooked. This will be very attractive for the malaria community but also for other parasitic diseases in which the spleen is involved. The team has developed a very good networking, and a good combination of clinical and applied research. The main strategies of the team are 100% in line with the overall philosophy of the CIMI.

- Weaknesses and threats:

It is likely that the scientific community will use the newly developed filtration system and the team needs more manpower to stay at the top of this research direction. This potential threat should be taken seriously.

- Recommendations:

The team is doing cutting edge science with novel approaches that will be attractive for other teams, with more resources and manpower. Therefore, in order to stay in a leading position, the team needs to recruit a full time researcher who will fully concentrate on the proposed project. The team should also try to attract foreign students and post-docs who will come with their own fellowships.

Team 5 : Strategies in vaccination and immunity

Name of team leader: Ms Behazine COMBADIERE

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	0	1	0
N2: Permanent EPST or EPIC researchers and similar positions	1	1	1
N3: Other permanent staff (without research duties)	1	1	0
N4: Other professors (PREM, ECC, etc.)	0	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	7	6	3
N6: Other contractual staff (without research duties)	1	2	0
TOTAL N1 to N6	**10**	**12**	**5**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	1
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

The team focuses on the skin as a route of vaccination. Its members are interested in needle-free vaccine administration via hair follicular targeting.

In the last five years the team has studied the immune memory to influenza and vaccinia vaccines in humans and found persistence of CD4+ cytotoxic T cells for at least 25 years after vaccinia vaccination. However, this is lost after HIV infection. The team has also proposed a bio-modelling analysis after pandemic influenza vaccination.

The team has compared antigen uptake and transport after different routes of vaccination and has used chemokines as adjuvants. The most original part of the work is the exploration of hair follicles for vaccination, which is explored for influenza in a FP7 project coordinated by the team leader.

Among the 26 papers produced since 2007, 12 were published by team members as leading authors, including a paper published in Immunity, J. Clin. Invest., and 2 in J. Invest. Dermatol. (#1 in dermatology).

Overall the activities of this team have been judged excellent, both by the original approaches taken and by the quality of the published papers.

Assessment of the unit's academic reputation and appeal

The team is coordinator of a FP7 program called CUT'HIVAC and has been successful in securing an impressive amount of national and international grants. The team leader has given many national and international conferences and is the recipient of a "prime d'excellence" 2012. The team has attracted foreign post-docs. This is thus qualified as being excellent.

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

The team has a strong involvement in translational research and has many contacts with industry. The team leader participates in several industry advisory boards on vaccines.

The team has participated in several clinical trials.

The team has organised seminars on biomodelling of immune responses, has invited several international speakers, and has communicated on vaccine issues to the non-scientific public.

Finally, the team leader has organized or co-organized several national meetings, but no international meeting.

Together this activity is thus judged as being very good to excellent.

Assessment of the unit's organisation and life

The team is composed of 2.5 permanent FTE scientists, currently trains 4 PhD students and 3 post-docs. 1.5 scientist FTE are not associated with papers of the team. This management structure is thus rather good, but could be improved by the stronger involvement of some of the scientists in publishable research.

Assessment of the unit's involvement in training through research

The team leader teaches 8-10 h at Master year-2 level per year and one of the team members has teaching charges as an assistant professor. Four PhD students have been trained, two of which have successfully completed their PhD. Both have published as first authors in good to excellent international journals. This training activity is thus excellent, especially considering the relative small size of the group.

Assessment of the five-year plan and strategy

1.5 permanent scientist FTE will be leaving, there are plans to recruit two CR, and a new professor will join the team.

The project will continue along the same lines as those that have already been successfully followed in the previous years, with major focus on skin immunization and the understanding of the mechanisms that may lead to long lasting immunity. In particular, the link between the skin and the mucosa will be explored. Humanized mice will be used. There will also be a strong focus on translational research, including clinical trials. Finally, several combinations of vaccination routes will be explored.

This project may have obvious far-reaching impact on public health. The team is ideally suited to bring the project to a successful outcome. The size of the team is appropriate, especially if the two CR can be recruited. This is thus an excellent strategic plan.

Conclusion

- Strengths and opportunities:

In line with the general strategy of the CIMI, this team is strongly focused on translational research. This should allow this team to have a major impact on vaccination strategies. In addition, the approaches taken by the team for vaccine delivery (using the hair follicles) are very original and have already shown their efficacy in different models.

The team has developed over the years an excellent expertise on immune memory, which may have major impact on future vaccine development strategies. As such, the team has already made significant contributions in the field. These contributions have led to a very good publication record, including papers published in Immunity and J. Clin. Invest.

The work of the team does also benefit from good collaborations at an international level, as exemplified by the coordination of a FP7 program by the team leader.

Finally, the team has been able to secure good funding and has many interactions with industry, which should allow the team to concretely pursue its scientific objectives.

- Weaknesses and threats:

For the moment, the team is still small, which may be a threat for the highly competitive work it is doing. The combination approach of different adjuvants and administration routes may potentially lead to unfocused developments.

- Recommendations:

There is good focus for the moment, and the team should be vigilant to stay focused. The research subject is highly competitive, and the team should try and recruit new scientists and increase the critical mass in order to stay at the forefront in its area.

Team 6 : Chemokines in Pathology and Inflammation

Name of team leader: Mr Christophe COMBADIERE & Mr Philippe DETERRE

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	0	2	0
N2: Permanent EPST or EPIC researchers and similar positions	3	3	3
N3: Other permanent staff (without research duties)	1.5	1.5	1.5
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	3	3
N6: Other contractual staff (without research duties)	4	4	4
TOTAL N1 to N6	**11.5**	**13.5**	**11.5**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	2	4

• Detailed assessments

Assessment of scientific quality and outputs

This team is co-directed by two senior researchers with a DR2 position, and, in addition, includes one researcher, two engineers (one IR and one IE) with INSERM permanent positions and one PU-PH and one MCU-PH (AP-HP), totalizing seven permanent members. The team also includes seven other non-permanent members: post-docs (three), PhD students (two) and engineers (two). Therefore, the team has reached a good equilibrium between permanent and non-permanent staff that should allow for the good accomplishments of the projects.

The research activities of this team are mainly focused on the study of the chemokine CX3CL1 and its unique receptor CX3CR1. One of its projects consists in investigating whether CX3CR1 single nucleotide polymorphisms are associated to inflammatory diseases. This team is also investigating the role of CX3CR1 in several experimental models of human diseases, mostly using CX3CR1-deficient mice as first approach. Last, these studies are completed by biochemical and structural analyses of CX3CL1.

The research activities of this team led to contributions in 41 publications (between 2007 and 2012), including two reviews. Most of them are from collaborative projects, and only 14 emerged from their own projects, which is about one publication per researcher per year. In general the publications are not in high profile journals (9 out of 14 are in journals with IF < 6).

In conclusion, even though this team is quite productive, it definitively needs to be more ambitious, more focussed, and needs to concentrate its efforts to dissect molecular and cellular mechanisms rather than studying a large panels of human diseases.

Assessment of the unit's academic reputation and appeal

The PIs got 12 speaker invitations at national and international conferences in the field of chemokines but also in meetings with a broader audience. However, the participation in meetings is not equal among the PIs. PIs have organized one international meeting in 2009.

Funding is regularly obtained from both French and European programs (AFM, UPMC, ANR & FP7).

Several collaborations exist, mainly with national partners. The partnerships are steady, generating publications over the years.

Since 2007, nine PhD students, and four post-docs joined the team. One previous PhD student was recruited as an INSERM junior researcher.

Therefore, this is a dynamic team that should however reinforce its international visibility by participating more in international meetings.

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

The team members participate in diffusing scientific knowledge to general public by writing and editing a book, by contributing to interviews broadcasted at public TV. Team members are also involved in a program of prisoner rehabilitation. PIs were members of several executive committees and one of the PIs will be the Director of the CIMI. The panel appreciates this team's efforts in diffusing scientific knowledge to a general audience.

Assessment of the unit's organisation and life

N/A

Assessment of the unit's involvement in training through research

Since 2007, this team has trained nine PhD students, three post-docs, nine technicians, and a dozen of master students. One of the PIs is teaching through seminars in several French Universities and he is participating in the program of three Masters. Therefore, this is a very active team.

Assessment of the five-year plan and strategy

The project aims at validating chemokine-based therapies as a new way of treatment of inflammatory diseases. This is a very challenging project since to date very few molecules targeting chemokines or chemokine receptors are on the market. To this aim, the team has planned to investigate the structural and functional analyses of two particular chemokines and chemokine receptors (i.e. CX3CL1/CX3CR1 and CXCL16/CXCR6), to develop therapeutic tools targeting CCR2 and CX3CR1, and to study the role of chemokine/chemokine receptors on subsets of leukocytes in human diseases (however no detailed project is described), and, finally, to investigate the role of chemokine/chemokine receptors using animal models.

This five-year plan is too exhaustive. It looks like a large screening of several animal models of human diseases in which CX3CR1 and its ligand may have a role. It lacks a real biological question that would definitively put this team at an internationally recognized level.

Conclusion

- Strengths and opportunities:

The team benefits from the strong expertise of the two leaders in the domain of chemokines and chemokine receptors. The newly recruited INSERM researcher (with expertise in two photon imaging) will certainly be an asset for investigating the role of chemokine/chemokine receptors in mouse models of human pathologies. The development of new chemokine antagonists may lead to promising anti-inflammatory drugs. Finally, the identification of *Plasmodium falciparum* proteins involved in the adherence of the infected red blood cells is very promising. This line of research is very competitive and well relevant to human health.

- Weaknesses and threats:

The projects are too ambitious. Too many projects are developed. The team's work remains too descriptive and involved mechanisms are insufficiently addressed. The team should develop tools and strategies to dissect the molecular and cellular mechanisms of action of chemokine/chemokine receptors of its interest. Finally, the team should definitively avoid the systematic "screening" of transgenic mouse lines.

- Recommendations:

This team has enough experience and skills in the field to develop more ambitious and focused objectives to become internationally competitive. The team should develop a deeper connection with other groups at CIMI working on *Plasmodium falciparum*. The arrival of a new theme should be a strength and not a cause of loss of focus, as it appears to be the case.

Team 7 : Cellular and molecular immunology of chronic inflammatory diseases

Name of team leader: Mr Guy GOROCHOV

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2	2	2
N2: Permanent EPST or EPIC researchers and similar positions	2	2	2
N3: Other permanent staff (without research duties)			
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	3	3
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**7**	**7**	**7**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2	3
Theses defended	3	3
Postdoctoral students having spent at least 12 months in the unit	3	3
Number of Research Supervisor Qualifications (HDR) taken	2	2
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

The team was composed of two independent groups, one working on the biology of human NK T cells ("NK cells and pathologies" group), the other studying the role of different cellular actors in chronic inflammatory diseases ("Immunoregulation and immunotherapies" group).

Over the past five years the "NK cells and pathologies" group has discovered a new ligand for NKp44 that plays a role in the HIV infection. It has characterised NK cell-reconstitution following hematopoietic stem-cell transplantation. Its work has led to four patents and the creation of a start-up company. Its publication record is very good with 22 publications signed as principal authors, these include two publications in Blood, two in PloS Pathogens, one in Proc. Natl. Acad. Sci. USA and all the others in good speciality journals (e.g. AIDS, Leukemia). The team is very active in the field of translational research. Based on its discoveries, it has created a start-up that will be dedicated to the development of new biotherapies for infectious diseases and cancer. This initiative was supported by governmental grants and has recently received support from AFSSAPS for a first clinical trial. This is an excellent scientific output for a relatively small team.

The "Immunoregulation and immunotherapies" group is slightly less focused, it addresses different immunological questions related to inflammatory diseases with a special focus on Lupus. Over the past five years it has contributed to the development of a new nomenclature for human regulatory T cells and it has characterised the T reg profile associated with different inflammatory diseases. It has contributed to the production of chemokine super agonist by a phage display approach. Finally, the group has studied the interaction between EBV reactivation and lupus flairs and it has demonstrated that CD8 responses against EBV are impaired in lupus patients. Its research activities has led to a large number of publications (119) mainly in speciality journals, the majority are not signed as senior authors by team members. This highlights the large number of collaborations in which the team is involved. The team leader and his principal investigators are, however, principal author on publications in high impact journals such as PloS Pathogens (one), Am. J. Pathol. (one), Autoimm. Rev. (one), and Immunity (one).

Overall this is a high quality scientific and translational production.

Assessment of the unit's academic reputation and appeal

Both groups are well known. The "Immunoregulation and immunotherapies" group members have been regularly invited for seminars in other departments in France or abroad. They have also participated in national and international congresses.

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

Both groups are excellent in terms of translational research. They have setup clinical trials. Seven patents have been obtained and a start up has been created based on the "NK cells and pathologies" group's discoveries.

Assessment of the unit's organisation and life

N/A

Assessment of the unit's involvement in training through research

Both groups are involved in teaching science and medical students. They are involved in the management of teaching either by organising courses or by being part of selection/organisational panels.

During this period the two teams have trained six master students and ten PhD students.

This demonstrates a high level of involvement in teaching and training.

Assessment of the five-year plan and strategy

The "Cellular and molecular immunology of chronic inflammatory disease" group is the follow up of the "Immunoregulation and immunotherapies" group. This group is engaging the next five-year plan with a reduced team in terms of full time investigators. The group working on the biology of human NK T cells is now applying to become an independent team of the future center. The majority of the investigators are clinicians (four Investigators are clinical practitioners, one investigator is a DR1), two engineers (IR) are completing the team.

It proposes to develop three lines of investigations.

The first project is in continuation with its previous work on regulatory T cell subsets. Its aim is to study the role of regulatory T cells in the onset of inflammatory diseases. The team will develop surface markers to characterise Treg and study the correlation between the quality of Treg population and the onset of different inflammatory diseases. It also aims at developing new in vitro culture systems to expand T reg cells. Its ultimate goal is to use these cells for therapy.

The second project is focusing on the role of Th17 in inflammatory diseases. The team will develop tools against CCR6 and it ligand CCL20, in order to target Th17 cells in inflammatory disease.

The third project is very ambitious as in collaboration with another group, this team aims to define the microbiome of patients affected by multiple sclerosis. The aim would be to identify a link between disease onset and a dysbioses. It will also characterise the antibody repertoire directed against the gut flora.

This is a very ambitious project that will need a reinforcement of the team in terms of full time researchers. Although all three subprojects are addressing inflammatory pathologies, they appear as rather unconnected. Taking into account the manpower of the team, some choices between the different projects might have to be done if the team is not reinforced.

Conclusion

- Strengths and opportunities:

Access to human samples from inflammatory disease affected patients allows them to be Involved in an ambitious project to study the microbiome of MS patients.

- Weaknesses and threats:

There are too many lines of investigations for the human resources currently present in the team.

- Recommendations:

The panel recommends making some scientific choices or strongly reinforcing the team.

Team 8 : Immuno-intervention and biotherapies

Name of team leader: Mr François LEMOINE

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	4	4	4
N2: Permanent EPST or EPIC researchers and similar positions	0	0	
N3: Other permanent staff (without research duties)	1	1	1
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	0	1	1
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**5**	**6**	**6**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	1	2
Theses defended	1	1
Postdoctoral students having spent at least 12 months in the unit	0	1
Number of Research Supervisor Qualifications (HDR) taken	0	2
Qualified research supervisors (with an HDR) or similar positions	1	3

• Detailed assessments

Assessment of scientific quality and outputs

This new team will focus its research on the development of innovative therapeutic strategies for head and neck cancers. Altogether the team members have published dozens of publications with various impact factors. There is little innovation in the research carried out, essentially applications of protocols for clinical research and trials.

Assessment of the unit's academic reputation and appeal

This team has the ambition to conduct applied research in oncology and the team seems to be already well established both in terms of staff and expertise. MDs and scientists are experts in their respective domains. Reputation remains at the local level and should be reinforced in the future in synergy with the CIMI.

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

The team leader is co-ordinator of a Centre of Clinical Investigation in Biotherapies (CIC-BT) and is involved in production activities in cell and gene therapy. This is a key point that would speed up the transfer of new therapy from the workbench to the patient bed. This is clearly one of the pillars of the CIMI.

Assessment of the unit's organisation and life

The research group is well structured with two associate professors, one with expertise in immunology, the other one with expertise in oncology and surgery. A good atmosphere was evident among individuals.

Assessment of the unit's involvement in training through research

The team is actively involved in teaching and training. The team leader has a strong track record in student training, heading University master and the University immunology department. The MDs contribute to teaching and training according to their University and Hospital duties.

Assessment of the five-year plan and strategy

The team leader presented one project focused on the treatment of head and neck cancer (HNSCC) patients. The project aiming at the development of a strategy for immunotherapy of HPV+ patients is ambitious and complex. The team leader presented interesting preliminary results with a HPV-16 E7 oncoprotein-vaccine produced by lentiviral vectors and plasma-retro virus-like particles (pVLPs). However, proof of principle remains to be demonstrated with appropriate models and therapeutic procedures combined with standard treatment, i.e radio-chemotherapy. The spontaneous tumour model based on the use of K14 HPV16 transgenic mice that develop tongue tumours seems to be a relevant model for the targeted disease.

The team leader presented alternative strategies, such as suicide gene derived from cytochrome p450 (CYP2B6-RED) that enhances the effect of cyclophosphamide. This strategy is complex and does not fit clearly with immunotherapy approach. This part of gene therapy of HNSCC is clearly distinct from the other parts of the CIMI scientific program.

In collaboration with other regional teams the team leader had initiated the evaluation of the PD1-PD1L blockade in TC-1 tumours to better control the tumour growth. There was no clear strategy on how to combine PD1-PD1L blockade with VLPs immunization, but there is clearly a great potential to improve CD8+ responses against HPV antigens in HNSCC patients.

Finally, the team leader introduces the evaluation of Dbait molecules, a class of DNA repair inhibitors triggering false DNA damage signalling in cancer cells. DNA repair inhibitors will be combined with standard chemo-radiotherapy and potentially with immunotherapy. Adequacy between this class of inhibitors combined with radio-chemotherapy and immunotherapy is not evident.

In conclusion the programme should be focused on combinations between HPV vaccine and standard of care used in HNSCC patrients

Conclusion

- Strengths and opportunities:

The team leader has a good experience both in academic research, as well as in biotechnology, heading GMP facilities and participating in clinical trials. The work presented here, not in itself very new, could have important benefits in HPV infected head and neck cancer patients. Despite the fact that HPV+ HNSCC patients have a better outcome than HPV negative patients in response to radio-chemo therapy, the relapse rate remains high and new immunotherapy strategies could have a strong impact in decreasing the number of non responders.

The evaluation of the vaccine in HPV16 transgenic mice that develop tongue tumours at 6 month of age when treated with 4-nitroquinoline-N-oxide will be highly informative and predictive of the efficacy of the product.

- Weaknesses and threats:

No targeted immunotherapy (therapeutic vaccine) is commercially available in cancer today and the domain remains challenging.

There are concerns about the relevance of the TC-1 (lung mouse cells) animal model for preclinical studies, which is not really an orthotopic model. Moreover, the TC-1 model is an "optimistic" model, as tumour cells still express MHC-I, which is not the case of HPV induced tumour in which class I molecules are down regulated.

VLPs have been used with success in prophylaxis but failed to cure established diseases.

P450 gene therapy is not so novel and does not relate so far with immunotherapy.

- Recommendations:

It is recommended to focus on the target immunotherapy strategy that would obviously bring benefits to the selected patient population. There needs to be a more clear clinical perspective for this immunotherapy project in HPV+ HNSCC patients and in particular a clear plan for the gene therapy part using the suicide gene approach and DNA repair inhibitors.

Team 9 : Immunobiology of viral infections and antigen-presentation

Name of team leader: Mr Arnaud MORIS

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1	1	1
N2: Permanent EPST or EPIC researchers and similar positions	1	1	1
N3: Other permanent staff (without research duties)	1	1	1
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2	2
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**5**	**5**	**5**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	1	2
Theses defended		
Postdoctoral students having spent at least 12 months in the unit	1	2
Number of Research Supervisor Qualifications (HDR) taken		1
Qualified research supervisors (with an HDR) or similar positions	1	2

• Detailed assessments

Assessment of scientific quality and outputs

This team is a young team, created in January 2009, that was initially affiliated to team #1. It was gradually established in the UMRS-945 INSERM, and in 2010 the group has been granted the label "Emergence Team" by the UPMC University. The team will be independent at the CIMI. To date, the team is constituted of two permanent researchers, one CNRS research director and one MCU (UPMC), together with non-permanent staff, constituted of 2 post-doctoral fellows, 1 PhD student, 1 technician and 1 master student.

The work of the team aims at deciphering the dual role played by immune cells in HIV replication/spread and in the establishment of immune responses.

Since 2009, the team has participated in ten publications, including one review. Among those, three were signed as first or last author by the team's PI. Two of these three publications are in high profile journals: J. Exp. Med. and PLoS Pathogens. Therefore, this is a very productive team that publishes in high quality journals.

Assessment of the unit's academic reputation and appeal

The team leader participates in several French and European collaborative projects. From 2010, he got several invitations in well-known Institutes, one speaker invitation in an International meeting, as well as a selection for oral presentation at a keystone meeting.

Funding is obtained from both French and European programs (Sidaction, ANRS, ANR & EU-FP7), and the PI is the coordinator of 6 projects.

Several collaborations exist within and outside the CIMI. Some of these partnerships have already generated publications. Since 2009, the team has already attracted one PhD student, two post-doctoral fellows and one technician. In 2010, one MCU of UPMC was also affected to the team, and in 2012 the team leader has been promoted DR2.

In conclusion, this team has a very good international visibility with a good appeal for students and post-doctoral fellows.

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

The team has contributed to the dissemination of scientific information to the public, notably by radio and TV interviews. In addition, the team is involved in the organization of seminars and lab visits for Sidaction donators.

Therefore, this team is really implicated in diffusing scientific knowledge to the general public.

Assessment of the unit's organisation and life

N/A

Assessment of the unit's involvement in training through research

Since its creation, the team has trained one PhD student, four master students, and other undergraduate students. Therefore, regarding the small number of full-time researchers and the youth of the team, this is a dynamic team that contributes well to the training of young researchers and students.

Assessment of the five-year plan and strategy

In the next five years, the team will continue in line with their previous accomplishments and will continue dissecting the links between HIV-induced PRR activation, MHC presentation, and the quality of T cell responses. The feasibility of the overall project may depend on the ability to increase workforce. More importantly, the panel has felt a lack of long-term vision with a long of a real ambitious project that will maintain the team to its highest level.

Conclusion

● Strengths and opportunities:

The team is a young team that is already visible internationally. It benefits of a strong expertise in cell biology of antigen presentation with a strong background in virology from the PI. The team has developed unique tools such as libraries of HIV-specific $CD4^+$ and $CD8^+$ T cells with strong national and international collaborations. The implantation of the team at the CIMI will allow it to have an access to human samples and to a cell sorter in an L3 room.

● Weaknesses and threats:

The numerous projects do not seem adequate with the small number of workers in the team. In addition, the projects are very competitive, and one can wonder whether they are original enough to keep up with the competition.

● Recommendations:

If the team does not succeed in increasing its workforce by recruiting at least one full-time researcher, it should refocus its projects. For example, while the T_{FH} project has been funded, it is very risky and in view of the numbers of full-time researchers in the team, workforce implicated in this project should maybe be reconsidered. In addition, the team should take better advantage of its libraries of HIV-specific $CD4^+$ and $CD8^+$ T cells by putting more workforce into this project.

The team has the competence and the qualities to be more aggressive in terms of funding. The team leader should therefore apply to competitive funding that will clearly increase his visibility, reputation and appeal.

The panel strongly recommends this team to be more ambitious.

Team 10 : Treg Biology and Therapy

Name of team leader: Mr Benoit SALOMON

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2	2	2
N2: Permanent researchers from Institutions and similar positions	2	3	3
N3: Other permanent staff (without research duties)	1	1	1
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	0	0	0
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	2	2	2
N6: Other contractual staff (without research duties)	0	0	0
TOTAL N1 to N6	**7**	**8**	**8**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	4	3

• Detailed assessments

Assessment of scientific quality and outputs

The team leader is an internationally recognized expert in T cell / Treg biology. He (co)authored several seminal papers in top journals reaching highest international standards, amongst those Nat. Medicine, Nat. Immunol., Immunity, J. Exp. Med., and other high-impact interdisciplinary journals. During the last funding period (2007-2012) two outstanding publications (5 year IF>14) amongst various papers should be mentioned, the 2010 J. Clin. Invest. and the 2010 J. Exp. Med. (with his team member as last author) publication, both -despite the short time span- showing already 30-60 citations each. After the completion of the CIMI report 2007-2012, another last author publication was accepted in the more specific journal "Diabetes" (IF>8). This is an excellent scientific output.

Assessment of the unit's academic reputation and appeal

The academic reputation of his team is very good, illustrated by several invitations to the team leader as chairperson during leading international events, such as the 2009 ECI Meeting in Berlin and the 2010 WIRM meeting in Davos. He has given plenary lectures at some of the most prestigious international scientific reunions such as the 2009 Keystone Meeting and is also nationally well received as speaker at numerous meetings. In addition, he (co-)organized several meetings and workshops in France and has initiated national and international collaborations (France, Germany, USA) with top-level scientists in the T cell and autoimmunity field. His laboratory is well funded with significant support e.g. from ANR and JDRF. The team leader is an active and visible member of the scientific community, also reflected by his duties as reviewer for international journals (J. Exp. Med., Blood, Eur. J. Immunol., J. Immunol. etc.) and French and international funding agencies (ANR, FRM, AFM, ARC, AP-HP, Israel Science Foundation, etc.). His team has attracted several excellent young French and international scientists, who could successfully build their careers on the training in his laboratory.

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

The team leader is very actively contributing to the dissemination of science, for example teaching high school students and giving lectures to high school teachers. The biggest medical, social and economic impact of his scientific work could possibly be his task as scientific coordinator of a phase I/II clinical trial testing the administration of Tregs in uveitis patients. This also very well funded trial is an outstanding example of translational research in immunology and might be a tremendous breakthrough for the Treg field as a whole. Additionally, the team has industry cooperation and funding as well as on-going patent applications, reflecting on the strong economic impact of his research.

Assessment of the unit's organisation and life

The team -within the new CIMI- has undergone structural changes with very successful colleagues joining other research structures as independent investigators and at the same time pioneers in the Treg field. The team appears to be very well organized with weekly lab meetings, joint meetings with colleagues from Cochin Institute and all the necessary infrastructure for successful scientific work.

Assessment of the unit's involvement in training through research

The team leader is currently teaching in seven different master programs, PhD committee member for 17 PhD students and supervised together with his team seven Master, five PhD students, and three postdocs since 2007. Some of the team members continued as postdoctoral fellows abroad, some obtained permanent positions as INSERM engineers or went to medical school. Also at the senior level, members of this team very successfully continued their careers, e.g. as independent DR2 scientists. This is an excellent implication in training through research.

Assessment of the five-year plan and strategy

The five-year plan of the TBT Team is ambitious, innovative and exciting. The re-structured TBT team within the CIMI gains important new and complementing input, especially in the area of signalling and Treg development. The scientific focus of the unit lays on medically highly relevant autoimmune diseases such as type I diabetes, uveitis, GVHD, atherosclerosis, and multiple sclerosis. The team has established all the necessary experimental systems and mouse models to generate important contributions to the field and nicely complement the CIMI as a whole. The translational aspect (phase I/II uveitis study) of the work program might be a potential milestone for the therapy of autoimmune diseases.

Conclusion

- Strengths and opportunities:

The focus of the TBT team on basic questions of Treg biology and cellular therapy of autoimmune diseases is a perfect mix of basic and translational research in immunology. Opportunities derived from the new CIMI structures can be expected based on new collaborations that should arise since excellent groups are being re-located and in close proximity to this team. For the translational work, the close collaboration with clinicians at CIMI is a major opportunity.

- Weaknesses and threats:

Although the focus of the group is relatively broad, aiming at different models of autoimmune diseases, this could be considered both as weakness and as strength, given that Tregs are involved in many inflammatory diseases and conserved mechanisms can and should be studied in various diseases. The main potential threat that could be observed during the site visit is the unclear situation about the lab space.

- Recommendations:

The TBT team may especially benefit from groups working on chronic infections (where Tregs have an important role) and might therefore consider more collaboration in this direction as well. The lab space situation should be clarified; ideally all CIMI teams should be in the same building. For future translational work, access to patient samples could be standardized (example of a "unified bio bank").

Team 11 : Molecular biology and immunobiology of malaria liver infection

Name of team leader: Mr Olivier SILVIE

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	0	0	0
N2: Permanent EPST or EPIC researchers and similar positions	1	1	1
N3: Other permanent staff (without research duties)	2	2	2
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1	1
N6: Other contractual staff (without research duties)	0	0	0
TOTAL N1 to N6	**4**	**4**	**4**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2	
Theses defended	0	
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	2	

• Detailed assessments

Assessment of scientific quality and outputs

The PI joined the CIMI in 2010 and is now leading his own group. Before, he received training in labs in Paris as a PhD student and as a postdoctoral fellow, and at the MPI in Berlin as a postdoctoral fellow. With this experience he is now well trained to investigate the exoerythrocytic stage of the malaria parasite with both the rodent malaria model but also with the human parasite *P. falciparum*. This is a very remarkable aspect and actually very rare among malaria researchers and puts him in a very good position in the field.

The PI has a good track record from his former position at the MPI in Berlin but so far he has not published any work performed at the Pitié-Salpétrière site. Since 2008 he has published seven papers, three as first or last author. The highest-ranking publication with him as a prominent author was in PLoS Pathogens in 2008. The quality of his work is very good. All together he has an excellent publication record and a very promising future in malaria research. All members of the committee were impressed by his performance and are convinced that the PI will become an important leader in the field of malaria research.

Assessment of the unit's academic reputation and appeal

The PI is still young and so far has not been invited to many conferences or by academic institutions. However, he has attended many conferences and his work is very well acknowledged in the field. His national and international fund raising is very good to exceptional. He is well connected in the field and has a number of international collaborators, which will help him to become more visible in the field of malaria research.

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

N/A

Assessment of the unit's organisation and life

N/A

Assessment of the unit's involvement in training through research

The PI has recruited two postdocs and two PhD students and has attracted several master students in the past. Since the team has also two permanent positions the structure of the team is very good. It is recommended that the PI becomes more visible to students to attract more master and PhD students. Together, training through research of this team is considered good.

Assessment of the five-year plan and strategy

The research project was very well presented. It is very well structured, very ambitious, and has clear goals. Most of the work will be done in collaboration with other teams at CIMI or international collaborators. It is safe to predict that the project will result in major breakthroughs in malaria research. Although the focus of the team is on basic research there are also aspects of translational research. Together, the team is very well integrated in the CIMI and has a great perspective.

The project has two main axes: mechanisms of sporozoite entry and regulation of parasite stage conversion. To address these issues the PI has generated very useful transgenic parasite strains. For the first axis the most important transgenic parasite strain generated is one that is defective in transmigration. This allows a much more accurate investigation of invasion because one does not have to distinguish between both events (transmigration and invasion) anymore. The PI has a long-standing expertise in research of sporozoite invasion. He described in a nice series of publications that the tetraspanin CD81 is required for *P. falciparum* and *P. yoelii* sporozoite invasion although CD81 has obviously an indirect effect. The goal is now to identify additional factors involved in invasion and the working hypothesis is that the parasite injects the receptors in the host cell to then bind to them with surface ligands. How this happens and how CD81 and other host molecules are involved will be addressed.

The second axis concentrates on the identification of novel parasite factors involved in parasite development in the liver. The PI has already published the discovery of the regulatory protein SLARP. Knockout of *slarp* gene resulted in the arrest of parasite development. Microarray analysis of SLARP-negative parasites and comparison with wild-type parasites revealed 150 genes down-regulated in SLARP-negative parasites. From these 150 genes 60 have been selected for further analysis. Selection criteria have been i) strong down-regulation and the ii) presence of homologues in the genome of the human parasite *P. falciparum*. 30 genes will be investigated by knockout approaches at the MPI in Berlin and 30 at CIMI. The phenotype of the parasites will be monitored and the parasite with a defect in liver stage development will be further analysed. This way it is hoped to finally being able to dissect the regulation of parasite stage conversion until the formation of merozoites, the infective stage for red blood cells. Together, this project is very well planned with clear goals and milestones. The PI provides solutions for possible problems. The perspective for this project is therefore extraordinary good.

Conclusion

- Strengths and opportunities:

The team has very good national and international funding and is very well integrated in the CIMI. It has excellent international networking. The PI is one of the very few researchers with strong expertise in human and rodent malaria models. This constitutes a very good basis for translational research. The PI is a dedicated malaria researcher with training in some of the best labs worldwide.

- Weaknesses and threats:

The team is still very young and the PI is not yet visible in the malaria community as a group leader with his own research direction. He is a very modest person who should more actively participate in scientific discussions at conferences.

- Recommendations:

It is recommended for the group leader to become more visible in the malaria community, attend and actively participate in important malaria meetings. The team should attract international students/postdocs. It should be careful not to be covered with collaborations, which earns co-authorships only. The team should make clear in the field what its research focus is and that the PI is more than a postdoc of his former internationally very recognized supervisors. The PI should envisage becoming member of the executive board at CIMI. This is important to get a good standing at the CIMI because this will also help him to become more visible in the field outside the CIMI.

Team 12 :

Identification and preclinical validation of novel therapeutic targets against malaria

Name of team leader:

Ms Dominique MAZIER & Mr Georges SNOUNOU

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2	2	2
N2: Permanent EPST or EPIC researchers and similar positions	2	3	3
N3: Other permanent staff (without research duties)	6	6	3
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	5	5
N6: Other contractual staff (without research duties)	1	1	0
TOTAL N1 to N6	**14**	**17**	**13**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	1	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	4	4

• Detailed assessments

Assessment of scientific quality and outputs

The major scientific achievements concern: (i) the origin and evolution of *Plasmodium falciparum* through phylogenetic analyses of the parasites, (ii) the pre-erythrocytic stage of parasite development, with the characterization of sporozoite entry mechanisms into hepatocytes and parasite factors involved in liver infection ; (ii) the blood-brain barrier disruption -an event leading to cerebral malaria- the team having shown that cytoadherence of *P. falciparum*-infected red blood cells perturbs endothelial function through apoptosis-induction and protozoan-triggered metabolic acidosis.

Team members were associated with approximately 150 articles published in peer-reviewed journals. Notably, a member of the team was the first or last author of 13 original papers issued in outstanding journals (*Blood* [five articles], *PLoS Pathogens* [three articles], *Cell Host & Microbe* [one article], *the Journal of Infectious Diseases* [four articles]), and a review in *Nature Reviews in Drug Discovery*. In collaboration with international research groups, the team also published three papers in *Science*, the *New England Journal of Medicine,* and *PNAS*.

Overall, the team produced high quality, basic research during the past for years, contributing to a better knowledge on malaria.

Assessment of the unit's academic reputation and appeal

The team has recognized expertise in its area and its visibility is excellent: (i) the team has been (is) a partner (mostly) or coordinator of several grants funded (with substantial financial supports) by international funding agencies (the NIH, the Gates Foundation, the European Union, the Wellcome Trust) and national funding agencies (the ANR and the Ministry of Higher Education and Research [LabEx]) ; (ii) four French senior scientists (two full-time researchers from Inserm and CNRS) joined the team and seven postdocs (some from abroad) were recruited during the past four years ; (iii) team members (two out of fourteen permanent senior scientists, including the team leader) have been regularly invited to give seminars and to present their work at various national and international institutes and meetings ; (iv) team members were requested as experts for international institutions (the WHO, the European Commission, the Medical Research Council,...) and as reviewers for outstanding journals (*Science*, *Nature*, *PLoS Medicine*, *Cell Host & Microbe*, *PLoS Pathogens*).

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

Some members of the team had clinical and medical laboratory activities and the team headed the National Reference Centre for Malaria, all activities being beneficial opportunities for research development.

As recognized expert in malaria, the team had sustained links with different pharmaceutical companies (Novartis, Sanofi-Aventis) for opinion and validation of new antimalarial drugs leading to industrial contracts.

Valorization of its research is a constant concern of the team and it deposited thirteen patents.

The team has been involved in many cultural events at the national level ("La Fête de la Science"; radio, live broadcast and journal interviews).

Overall, the unit's interaction with the social, economic and cultural environment is excellent.

Assessment of the unit's organisation and life

Good governance was noted during the visit unit, one co-director of the team (leader of the previous team) having encouraged two talented senior scientists to become independent (and they did as they created their own team).

Assessment of the unit's involvement in training through research

Seven students obtained a PhD during the past four years; three doctors got a job in private companies (including innovative consulting and start-up) and three others have a postdoctoral position abroad (Thailand, Singapore and Gabon). At present, the team hosts five postdocs and three PhD students.

The team coordinates a parasitology-mycology program in the Master "Cellular & Molecular Biology" (Pierre & Marie Curie University).

In conclusion, training through research is excellent.

Assessment of the five-year plan and strategy

The project, in continuity with the past, is well-focused: it confers competitiveness in a highly competitive field of research. Discovering novel therapeutic strategies to control malaria is the general objective of the team. It specifically aims: (i) at unravelling the pathways leading to quiescence (for extended periods of time) and reactivation of hepatic parasite forms known as hypnozoites, a rational basis for drug discovery; (ii) at identifying the protective antigens of sporozoites for developing acellular vaccines against the *Plasmodium falciparum* pre-erythrocytic stages; (iii) at evaluating protection of endothelial cells from the protozoan-induced endothelial damages by antibodies directed against *Plasmodium* apoptosis-linked pathogenicity factors (PALPFs) or inhibitors of specific signalling pathways (fasudil, atovarstatin).

The team has scientific and technical skills (especially in the *Plasmodium* hepatic stages), access to local facilities (genomics/post-genomics and proteomic platforms, insectarium, cell imaging, flow cytometry and animal facilities), collaborations and substantial funding that render project implementation credible.

Overall, an outstanding, basic research project, with a strong potential for medical application is proposed for the next five years.

Conclusion

- Strengths and opportunities:

The team has an excellent track-record of scientific productivity and international visibility, and its research program for the upcoming five years is solid and paves the way to new therapeutic strategies.

The team has an internationally recognized expertise in the pre-erythrocytic stage of *Plasmodium* development and is the only laboratory throughout the world able to routinely culture parasites in primary hepatocytes. In addition, the team has access to state-of-the art facilities (including an insectarium) and has substantial funding for research development.

- Weaknesses and threats:

The team is relatively small (however, the project is well focused) and the research area is highly competitive.

- Recommendations:

Two out of the four permanent senior scientists will be retired in 2018 and consequently, it is important that the team leader recruits young, talented researchers during the upcoming five years.

Team 13 :

Mechanisms of emergence and diffusion of multiple drug resistance in Mycobacterium tuberculosis and Enterobacteriaceae

Name of team leader:

Mr Wladimir SOUGAKOFF

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	11	11	11
N2: Permanent EPST or EPIC researchers and similar positions	0	0	0
N3: Other permanent staff (without research duties)	4	3	3
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	0	1	0
N6: Other contractual staff (without research duties)	5	5	2
TOTAL N1 to N6	**20**	**20**	**16**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	5	
Theses defended	8	
Postdoctoral students having spent at least 12 months in the unit	0	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	5	5

• Detailed assessments

Assessment of scientific quality and outputs

The team has published a number of important results in the fields of tuberculosis epidemiology, antibiotics resistance in mycobacteria, and molecular biology of selected drug targets (DNA gyrase, ATP synthase). A total of more than 115 papers has been published during the period (more than 80 for the former head of unit; about 20 for the future head of unit), mostly in specialty journals of international standard (e.g. Int J Antimicrob Agents etc). A few papers have been published in broader journals (e.g. PLOS One, J Bacteriol). A major advance has been made in experimental chemotherapy using TMC207 (Am J Respir Crit Care Med, IF 11). The work is well cited (190 citations/year for the former head of unit, 67 for the future head of unit). Overall, the team produces important results that translate into a insufficiently high publication level.

Assessment of the unit's academic reputation and appeal

A few invitations to communicate/participate to national/international events are reported (e.g. ECCMID 2009, Euro-TB network). A few awards (e.g. 3 ICAAC Infectious disease fellows grant programs, two ESCMID Research grant awards) were obtained by members of the team. One (french) postdoc was recruited. A total of seven recruitments of (French) medical practitioners and clinical technicians were made during the assessment period. Visibility at international events and attractiveness to international researchers/post-docs are not sufficient.

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

The team is clearly a reference in the field, on national and european levels. The number of industrial contracts is impressive, with over ten industrial grants during the period. In total, 1.8 M€ fund were raised during the period. This is remarkable. Visibility to the public is great, on national level. The impact on TB treatment (TMC207) and management of antibiotic resistance on national level (NRC) is important. Clinical activity and coordination of clinical experts groups on national level is important.

Assessment of the unit's organisation and life

Because the staff is deeply involved in clinical activity and teaching, post-docs and PhD students as well as full-time researcher(s) (e.g. Inserm or CNRS CR1, DR2) should be hired to conduct the proposed research. The team encompasses many permanent clinical staff, all of whom may not be involved in research activity. Having less permanent staff in the team would allow recruiting more students and post-docs as well as permanent scientists. The team should seek more benefit from CIMI infrastructures and expertise (e.g. animal models, immunology, etc.).

Assessment of the unit's involvement in training through research

A total of eight PhD students were trained during the period. The teaching activity is intense on national level (Master, medical students etc). Participation to international training events (ESCMID postgraduate course 2011) is occasional. The post-graduate career of the PhD students trained by the team is difficult to evaluate, and should be better highlighted.

Assessment of the five-year plan and strategy

The team results from the fusion of two UMPC research units. The project is in continuation with previous activity: molecular mechanisms of resistance in mycobacteria and enterobacteriaceae. The projects may be over-ambitious (genome-wide analyses etc.) and should be carefully monitored (e.g. the choice of strains to be sequenced should be carefully made). Meeting points should be found between the two projects (e.g. this could involve investigation on TA systems in mycobacteria and enterobacteria). The team should be more embedded in international groups through funding agencies & international collaboration consortia.

Conclusion

- Strengths and opportunities:

Access to vast collections of clinical isolates and mutants is a bonus that should be better exploited in the context of national and international collaborations, including within CIMI, to explore host-pathogen interactions in cell and animal models.

- Weaknesses and threats:

The huge number of permanent staff with heavy clinical and teaching duties, and the low number of students and postdocs and absence of permanent scientists is of concern. This translates into the level of publications; there are many publications, but few (if any) in high impact journals.

- Recommendations:

The team should down-size the number of permanent staff and involve more students, postdocs and permanent scientists (e.g. CR, DR) to conduct the many and ambitious projects proposed. The team should be more aggressive in its publication and communication policy. Visibility should be increased, at an international level, through participation to international conferences, and to international research consortia (e.g. EU projects on drug resistance in mycobacteria or Gram- bacteria etc.).

Team 14 : NK cells and pathologies

Name of team leader: Mr Vincent VIEILLARD

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	2	2	2
N2: Permanent EPST or EPIC researchers and similar positions	1	1	1
N3: Other permanent staff (without research duties)	0	0	0
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	0	0	0
N6: Other contractual staff (without research duties)	1	1	1
TOTAL N1 to N6	**4**	**4**	**4**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	0	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs

Over 2007-2012, this team has developed research projects focused on the role of Natural Killer (NK) cells in immunopathologies which included fundamental, translational, and clinical research.

The contribution to the field of NK cell biology has been significant. This is reflected by the publication of a total of 32 publications for the head of the team, with 19 as first or last author. Among those 19 articles, some have been published in journals with high impact factors (PNAS, Blood, Plos Pathogens).

The main achievements include the development of innovative vaccine strategy for HIV-infected patients based on their identification of the ligand of NKp44 induced by the motif 3S of gp41; the study of NK cell reconstitution after allogenic hematopoietic stem cell transplantation and unrelated cord blood transplantation; the clinical assay of infusion of mature NK cells in patients with acute leukaemia, and the characterization of a modulation of the NK cell receptor repertoire during viral infections (HIV, cytomegalovirus, Chikungunya, Hepatitis B) and autoimmune disease (systemic lupus erythematosus).

The strength of the team resides in its capability to develop projects up to the clinic. They also have developed strong links with clinicians and therefore have access to cohorts of patients. In addition they have developed strong partnerships with industry.

The scientific quality of the work produced by the team is acknowledged and particularly their effort to study NK cell in human diseases and to develop innovative vaccine strategies.

Assessment of the unit's academic reputation and appeal

The work performed by the team is internationally recognized but it should be more visible. Despite the quality of the research, the head of the team has not been invited very often to speak at international meetings. Only French PhD and postdoctoral fellows have been recruited over 2007-2012. The team should make more efforts to communicate at an international level.

At a national level, the team has acquired a strong reputation and good visibility.

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

The economic impact of the research activity of the team is extremely high: they have filed five patents and they are founders of Innavirvax created in 2008. This company develops clinical trials based on the team's findings and contributes to the funding of the laboratory in terms of staff and consumables. This start-up won the contest of the young innovative start-up from the French Ministry of Higher Education and Research in 2008.

The team's involvement in clinical trials is also a hallmark of its activity.

Assessment of the unit's organisation and life

The team is well integrated in the new unit. It has already established collaborations with several of the teams which led to publications with shared authorships. It will pursue these tight collaborations in the next five years. The projects of the laboratory fit with the three axes proposed by the unit: "investigating to fight diseases", "investigating host-pathogen interactions" and "innovating in vaccinology and biotherapies", and it can thus play an important and specific role in this new structure.

Assessment of the unit's involvement in training through research

The lab has hosted five PhD students, three are now post-doctoral fellows and two obtained permanent positions. It has also trained several master students over 2007-2012. Several members of the team have been actively involved in teaching to M1 and M2 students. This underlines an excellent commitment of the team into training and teaching.

Assessment of the five-year plan and strategy

The projects of the next five years are a continuation of produced activity. The researchers propose 1) to further characterize NKp44L and assess its potential as a target for immunotherapy, 2) to go deeper into the mechanisms leading to viral modulation of the NK cell receptor repertoire, 3) to evaluate the role played by NK cells in chronic infections and 4) to test the efficacy of infusing NK cells in tumor models.

The projects are ambitious and can rely on solid background and strong collaborations with the clinic and industry. The strategy is to exploit the team's expertise, the tools it developed, and the established national and international collaborations to assess the role of NK cells in pathologies and how they can be used in therapy. The approaches are straightforward and should lead to success. The team has secured substantial funding although it will need to pursue its efforts to get more. The structure of the laboratory is adequate for the project proposed.

Besides finalizing ongoing projects, it may have been wise to include long term projects emerging from the current ones. It is indeed important to already build for the long term future.

Conclusion

- Strengths and opportunities:

The strength of the team is its strong focus on NK cell biology and the evaluation of the clinical impact of NK cells. The team has successfully developed projects from discovery up to clinical applications. Its work has yielded major breakthroughs, in particular related to NKp44 Ligand.

The team has developed strong industrial partnerships and has been involved in the foundation of a bio-pharmaceutical company.

The team is key to the new unit for its expertise on NK cells and its clinical and industrial research activities.

- Weaknesses and threats:

The team has based its strategy for the next years on previously established projects that it should successfully complete. However, it may lack creative prospects as it may not develop novel areas of research that could yield projects on a long-term basis.

Competition on the first project "modulation of the NK cell receptor repertoire" is strong and the team might have difficulties to compete at an international level.

- Recommendations:

It is recommended to the team to communicate more at an international level to increase its visibility and competitiveness.

It is also recommended to the team to revise slightly its strategy for the next five years and include creative prospects in order to build for the future.

5 • Conduct of the visit

Visit dates:

Start:	Tuesday, February 12th 2013 at 8AM
End:	Wednesday, February 13th 2013 at 6PM

Visit site:

Institution:	Faculté de Médecine
Address:	91 Boulevard de l'Hôpital, Paris

Conduct or programme of visit:

Tuesday, February 12th 2013

Time: from 8:00 to 8:30	Door-closed meeting: Committee members and AERES representative
Time: from 8:30 to 9:00	Presentation by the head of the unit: past activity and projects
Time: from 9:00 to 9:45	Team 'Identification and Pre-Clinical Validation of Novel Therapeutic Targets against Malaria' (heads: Mr Georges SNOUNOU / Ms Dominique MAZIER)
Time: from 9:45 to 10:30	Team 'Parasites, Erythrocytes and Pathogenesis' (head: Mr Pierre BUFFET)
Time: from 10:30 to 11:00	Coffee break
Time: from 11:00 to 11:45	Team 'Molecular Biology and Immunology of Malaria Liver Infection' (head: Mr Olivier SILVIE)
Time: from 11:45 to 12:30	Team 'Immune-intervention and Biotherapy' (head: Mr François LEMOINE)
Time: from 12:30 to 13:30	Lunch-buffet
Time: from 13:30 to 14:15	Team 'Strategies in Vaccination and Immunity' (head: Ms Béhazine COMBADIERE)
Time: from 14:15 to 15:00	Team 'Immunobiology of Viral Infections and Antigen Presentation' (head: Mr Arnaud MORIS)
Time: from 15:00 to 15:45	Team 'Mechanisms of Emergence and Diffusion of Multiple Drug Resistance in Mycobacterium tuberculosis and Enterobacteriaceae' (head: Mr Wladimir SOUGAKOFF)
Time: from 15:45 to 16:15	Tea-break
Time: from 16:15 to 17:00	Team 'Persistent Viral Infections' (head: Mr Henri AGUT)
Time: from 17:00 to 17:45	Team 'NK cells and Pathologies' (head: Mr Vincent VIEILLARD)

Wednesday, February 13th 2013

Time: from 8:00 to 8:45	Team 'Chemokines in the Pathology and Inflammation' (heads: Mr Christophe COMBADIERE/ Mr Philippe DETERRE)
Time: from 8:45 to 9:30	Team 'Cellular and molecular immunology of chronic Inflammatory diseases' (head: Mr Guy GOROCHOV)
Time: from 9:30 to 10:15	Team 'Treg Biology and Therapy' (head: Mr Benoit SALOMON)
Time: from 10:15 to 10:45	Coffee-break
Time: from 10:45 to 11:30	Team 'Anti-viral and Vaccinal Immunity and Immunogenetics' (head: Ms Brigitte AUTRAN)
Time: from 11:30 to 12:15	Team 'Immunopathogenesis of Viral Infections and Immune Aging' (head: Mr Victor APPAY)
Time: from 12:15 to 13:30	Lunch-buffet
Time: from 13:30 to 14:00	Meeting of the committee with representatives of the University Paris 7, the INSERM, and the CNRS
Time: from 14:00 to 14:45	Three parallel meetings of the committee with: • PhD students and postdoctoral fellows • engineers, technicians and administrative assistants • researchers with permanent position (except the unit's director and team-chiefs)
Time: from 14:45 to 15:15	Closed-door meeting of the committee and AERES representative with the unit's director
Time: from 15:15 to 18:00	Closed-door meeting of the committee and AERES representative

Specific points to be mentioned:

Mr Andy WATERS was unable to participate to the site visit.

6 • Statistics by field: SVE on 10/06/2013

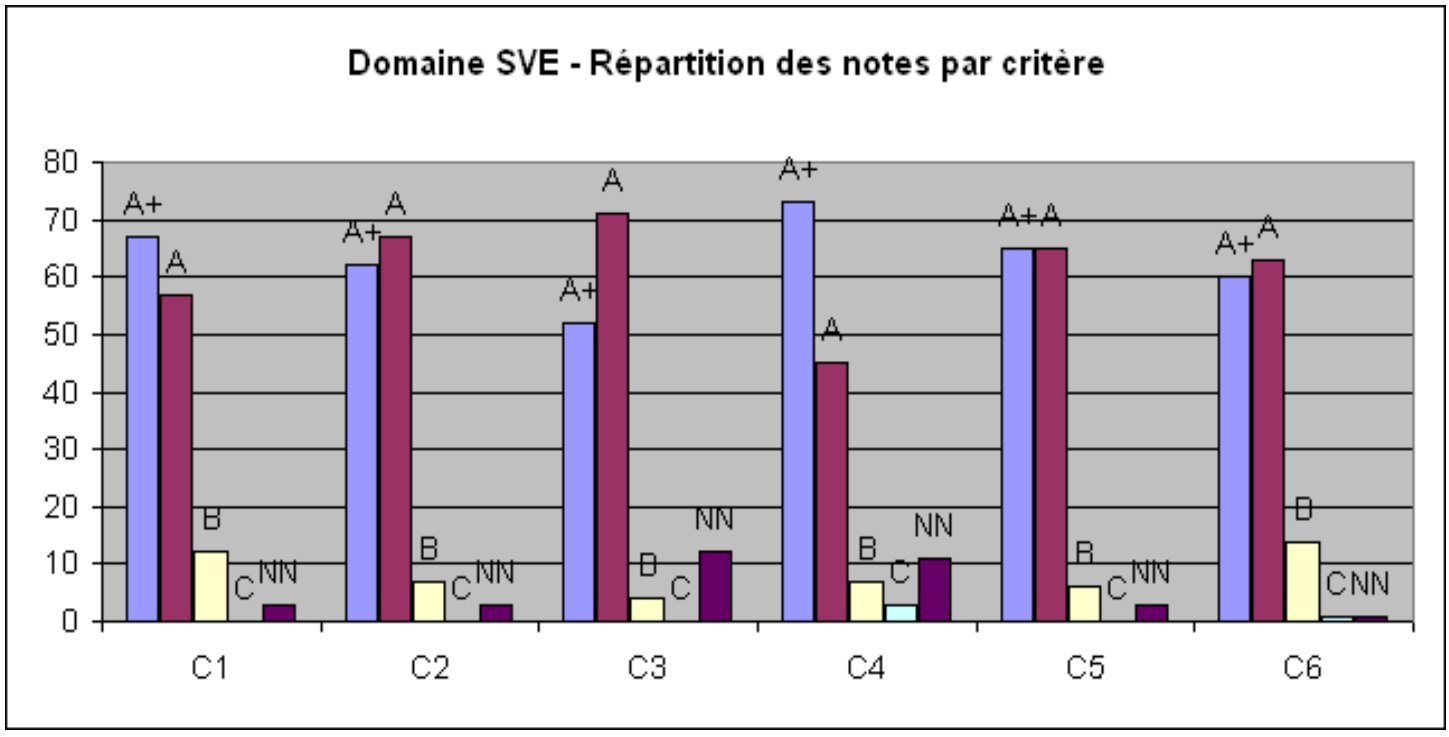
Grades

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	67	62	52	73	65	60
A	57	67	71	45	65	63
B	12	7	4	7	6	14
C	0	0	0	3	0	1
Non Noté	3	3	12	11	3	1

Percentages

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	48%	45%	37%	53%	47%	43%
A	41%	48%	51%	32%	47%	45%
B	9%	5%	3%	5%	4%	10%
C	0%	0%	0%	2%	0%	1%
Non Noté	2%	2%	9%	8%	2%	1%

Histogram



7 • Supervising bodies' general comments

Paris le 22 04 2013

Le Président
Didier Houssin
Agence d'évaluation de la recherche
et de l'enseignement supérieur
20 rue Vivienne - 75002 PARIS

M. le Président,

Nous avons pris connaissance avec le plus grand intérêt de votre rapport concernant le projet du Centre immunologie et des maladies infectieuses (CIMI), porté par M. Combadière. Nous tenons à remercier l'AERES et le comité pour l'efficacité et la qualité du travail d'analyse qui a été conduit.

Ce rapport a été transmis au directeur du laboratoire qui nous a fait part en retour de ses commentaires que vous trouverez ci-joint. Nous espérons que ces informations vous permettront de bien finaliser l'évaluation du laboratoire.

Restant à votre disposition pour de plus amples informations, je vous prie de croire, M. le Président, à l'expression de mes salutations respectueuses.

Le Vice -Président Recherche et Innovation

Paul Indelicato

Vice-présidence Recherche et Innovation
Tél. 01 44 27 20 09
www.upmc.fr

We are grateful to the AERES visiting committee members for their critical appraisal of our proposal to form a CDR and of the teams that it would comprise.

"It is essential that the CIMI strongly considers the recruitment of new, external teams. This is very important for its future development."

We have already had three groups who were very keen to join the CIMI, and we know of a few others who have considered it. We are aware of how important this will be to the future of the CIMI.

Our main obstacle, if not the only obstacle, is the question of laboratory and office space.

"There should be a clear strategy on how laboratory space and technical support is allocated to the different teams."

Laboratory space is a perennial issue. As it stands we do not have an urgent space problem, except with respect to welcoming new teams. We face two specific difficulties. First, the CIMI teams are dispersed in different floors and buildings on site. Second, space allocation depends on three authorities, the UPMC, the Faculté de Médecine, and the APHP. As a group, the CIMI teams have already made considerable efforts to propose a drastic reorganization of the space they currently occupy. The predominant philosophy is one of common shared laboratory space, and a rationalization of the office space (this has required some effort as it went contrary to deep-rooted previous practices). We are confident that this will allow us to make optimal use of the space we have. Furthermore, it will promote exchange between different team members. We have been promised a space of 230m^2, but it is not clear which year this will be delivered, and as a matter of fact, exactly where they will be located. This illustrates the administrative difficulties we face with respect to long-term planning of space. We are striving to bring all the teams close together in the same building, but there is no guarantee of success. A final, but important obstacle is the financial support to refurbish and in some cases bring the space and the amenities to legal standards. We have already made a number of funding requests to this effect (INSERM, regional government, charitable foundations). We hope that this AERES evaluation will stimulate the UPMC to contribute. A CIMI sub-committee specifically dedicated to this issue has already been formed and it has already made concrete proposal and plans to:

- Define optimal team module space based on Full-time equivalent (FTE),
- Increase common areas dedicated to specific activities such as cell culture (P1/P2/P3 labs), biochemistry or molecular biology,
- Rationalize office space.

"Some of the teams should try to publish in higher impact journals and strengthen their international visibility by participating in international networks, programs, and other events. (…) There should be a collective effort to apply for ERC grants and other EU projects."

We could not agree more. These recommendations are in perfect accord with the ambition of the CIMI, which is to promote quality of research and to become an international reference centre in Immunology and Microbiology. The CIMI is very much aware that international visibility and high quality in science go hand in hand. We intend our strengths to be based on

the interactions between basic and clinical research, as well as between immunology and microbiology. We believe that integration of biology and medicine will foster and ensure quality, originality and innovation. We are confident that as the integration between the various themes becomes organic, the scientific output will improve in quality and in impact. We will rely on a broader, more international Scientific Advisory Board (SAB) to keep us on the right track. Every two years all the teams will be evaluated internally as well as by the SAB. Their recommendations will be the main springboard for a proactive approach to bring the teams that had strayed, back to scientific excellence.

A recurring theme/worry was the low number of young tenured researchers who would ensure continuity. We are acutely aware of this problem, but we do not feel it is specific to the CIMI, but rather reflects a nationwide situation, where recruitment to permanent positions has dwindled to a trickle and where financial support of the research councils (INSERM, CNRS) and the universities is at low ebb. We are also concerned that a substantial number of senior staff will relinquish their team leaderships during the 2014-2018 period. We are convinced that these responsibilities will be taken up by some or many of the excellent researchers that have already expressed an interest in joining the CIMI, as well as by some in-house researcher many of whom are of exceptional quality. We expect that persons of quality from France and abroad will be attracted to join the CIMI as it becomes active and as its reputation spreads.

"The SAB should be made more international."

The composition of the SAB will be changed in accordance with this advice. We expect to have at least half of the members to be non-French scientists working outside France.

"Administrative staff should be increased. This will be important especially if the CIMI will be a Centre of three institutions (University, CNRS, INSERM)."

An Inserm-appointed person (IR) will join the CIMI as a chief administrative officer. We hope that our hosting institutions will also appreciate the crucial importance to the success of the CIMI of appointing full-time permanent staff to help the CIMI with human resources, project administration, and finances.

" The executive committee should include all 14 team leaders to take the essential decisions. It is essential to elect a deputy director (not a "co-director"), because the workload will be too heavy for a single director."

We do not disagree with either point. We feel that there has been a misunderstanding of the Management Regulations we had proposed (see points 4.3 et 4.4 in the "Charte"), but also that some changes were needed. The essential decisions will be taken by a committee in which all 14 teams are represented, usually by their head. We were not clear enough in our initial document, and some clarification is required with respect to the governing structure. The nomenclature we had chosen previously was possibly inappropriate.

We propose, now, that the governance will rely on a four-level governing structure: a) the Director, b) an Executive Committee that will be composed by a representative from each teams; this is the group who can take strategic decisions, c) a CIMI Council who will be composed of representative of all the teams as well as representative from each of a number

of different groups within the CIMI (students, technicians, post-doctoral scientists, senior scientists, clinical staff, etc…), d) the General Assembly (all the CIMI personnel).

The Director, the Executive Committee and the CIMI Council have agreed to the creation of a college of three elected deputy Directors (any CIMI staff with a permanent position is eligible) who, with the Director and the Chief Administrative Officer, will be responsible to implement and pilot the decisions made by the Executive Committee.

Team 1 Henri Agut

We thank the committee for their comments and recommendations.

Team 2 Victor Appay

We thank the AERES committee for their appraisal. In line with the committee's recommendations, our team is indeed focusing increasing efforts into investigating mechanistic aspects. Our work on the molecular basis of CD8+ T cell efficacy against HIV (recently published in Immunity - March 2013) is an illustration of these efforts.

Team 3 Brigitte Autran

We thank the committee for their comments and recommendations.

Team 4 Pierre Buffet

We thank the committee for what we perceive as an encouragement to continue and further optimize our approach. This positive evaluation should facilitate the recruitment of a permanent scientist as lack of manpower is, as wisely stated, a major threat to the project. The close correspondence of our approach with the CIMI philosophy being now acknowledged, we are confident that internal support will be granted to move forward. The committee wrote rightly that a second post-doc has been hired, but this position is essentially to help the PI handle projects linked to activities related to the Worldwide Antimalarial Network. Our first-line candidate for a CR1 application is one of the very few individuals with in-depth experience on the highly specialized field of red blood cell biomechanics and with experience in integrative research (I Safeukui). Because recruitment as CR1 is highly competitive and may take time, we will explore complementary ways such as initial limited-term contract on external funding or hiring a permanent searcher looking for a new position.

Team 5 Béhazine Combadiere

We thank the committee for this very positive comment.

Team 6 Christophe Combadiere and Philippe Deterre

We thank the committee for their comments and recommendations.

We would like to precise that 24 publications (and not 14 as mentioned by the reviewing committee) emerged of our team and 15 were collaborative works. The members of the team have recently published in high profile journals; J. Clin. Invest 2007 (IF~15, citation =132), J. Exp. Med. 2007 (IF~13, citation =113), Blood 2007 (IF~10, citation =16), Circulation 2007 (IF~14, citation =130), J. Clin. Oncol 2008 (IF~18, citation =23) and Immunity 2010 (IF~21, citation =55). Our efforts in the future will allow us to be more ambitious but also more focused on specific cellular and molecular issues.

Team 7 Guy Gorochov

We thank the committee for their comments and recommendations.

Team 8 François Lemoine

First of all, our team would like to thank the visiting committee for their evaluation, comments and recommendations. However, we would like answer to some comments.

The committee has pointed out *"**little innovation in the research carried out**" and "**reputation remains at local level**"*.

Concerning these two assessments, we would like to recall that our team is mainly involved in translational research and the implementation of clinical trials. Actually, team 8 is not devoted to a very basic research and is not structured for such a goal. The composition of the team with clinician and surgeon that follow one of the largest cohort in France of patients with head and neck cancers in parallel with the development of animal tumour models give us a strong opportunity to develop immunotherapy strategies from bench to bedside. The link of our team to the centre of clinical investigation in Biotherapies (CIC-BT) is crucial for speeding up our research toward clinical development. As our team is very recent, we have chosen to develop our research in collaborations with scientists with whom we have already successfully collaborated and which are not too far in order to facilitate the scientific exchanges. We are aware that it would be important to develop international collaborations in order to increase our visibility and particularly to raise European grants, but we have first to reinforce our publications in this new field. Then, our next step will be to develop international collaborations.

The team leader is well known in France and Europe in the field of Biotherapies as he has been one of the founder and past-president of the French Society of Cell and Gene therapy, member of the scientific editorial board of "Human gene therapy", director of an international master program in the Biotherapies and Immunology, member of the board of the French Society of Immunology and president of the CNU of Immunology. This will be helpful to improve the international reputation of the team.

The committee has also pointed out *"**the programme should be more focused**"*. It is clear that our relatively small team cannot handle all the aspects of cancer immunotherapy. The

main focused objective we have chosen to develop concerns the development of targeted therapeutic cancer vaccines. However, we are convinced that therapeutic vaccines alone would be not efficient enough to treat patients and should be combined with either standard and/or other innovative therapies. That is why we are also involved, but with a minor participation, in other research complementary programmes where we are offering our specific know-how.

Team 9 Arnaud Moris

We would like to thank the panel for the comments and the recommendations. We fully agree with the panel that increasing workforces will be detrimental to keep our research at the highest levels in a very competitive environment. We already identified a candidate with exceptional expertise that we fully support for a full-time researcher position.

We would like to stress the point that our overall and long term goals are to define cellular pathways involved in the processing of viral antigens in human cells. As emphasis by the panel, we have developed unique tools, e.g. a library of human anti-viral CTL and CD4+ cell clones that allow dissecting the processing of viral (HIV) antigens in infected cells. Much remains to be learned in the field of antigen presentation and to our knowledge very few labs use human primary cells infected with pathogenic viruses to address these issues. Our tools (HIV mutants, shRNA, etc.) and expertise in virology are clearly assets to make breakthroughs. For instance we discovered and characterized new cryptic HIV antigens and demonstrated that the antiviral factor APOBEC-3G enhances CTL recognition of HIV-infected cells, thus linking innate and adaptive immunity.

Our on-going and future work, at the edge of virology and immunology, is divided in two main axes:

1. we will decipher how signals and effectors of the innate immunity influence the expression and presentation of cryptic and classical MHC-I antigen to CTL. The kinetics of antigen expression, degradation and loading (in sum the quality of antigen presentation) most likely determine early elimination of infected cells.
2. we are currently deciphering new cellular pathways involved in the presentation of intracellular viral antigens to CD4+ T cells. Our work revisits textbook dogma stating that MHC-II molecules present solely extracellular antigens.

This work will bring new insights in immunology, virology and cellular biology. It is also of utmost importance for vaccine design.The project on Tfh supported by the ANRS, as it stands, is a short-term exploratory aspect of our work but perfectly integrates into the translational research of the CIMI. Our long-term goal is to derive from these unique samples HIV-specific Tfh and B cells to study antigen presentation in the context of B and Tfh interactions. We agree with the panel that our capacity to increase workforces will be detrimental for the development of this project.

Overall, we believed that the points mentioned above were clearly described in the detailed project submitted to the panel. Evidently, the oral presentation failed to put into perspectives these long-term goals.

Concerning the fundings, we are partners in three new grant applications submitted to the ANRS and we coordinate a grant application submitted to the ANR. We aim at using this ANR program as a core to set up an EU consortium. These projects integrate into our two main axes of research (described above).

Team 10 Dominique Mazier and Georges Snounou

We thank the committee for their comments and recommendations.

Team 11 Olivier Silvie

We would like to thank all members of the visiting committee for taking the time to assess our research program and for their positive comments. As recommended by the committee, increasing the visibility of our emerging team will be a priority. Whilst the team leader continues to collaborate with his former supervisors, he is now developing his own research lines, combining genetic approaches to explore sporozoite host cell invasion and spatio-temporal compartmentalization of parasite antigen presentation.

Members of the team have started and will continue to participate in major international parasitology meetings, including Woods Hole Molecular Parasitology Meeting and EVIMalaR annual conference. The PI is a member of the French National Parasitology LabEx ParaFrap, launched in 2012, which will allow recruitment of international fellows through the LabEx International PhD and Postdoctoral programs. In addition, the PI has been regularly teaching to Master students at the University Pierre et Marie Curie and AgroParisTech engineer school. In the past two years, 4 students from these institutions have joined the group for 2-6 months research training, and 2 PhD students from UPMC have been recruited in 2012, including a former Erasmus Master student.

This strong commitment in both research and teaching programs should help us developing cutting edge projects on malaria liver infection and becoming more visible in the field of malaria research.

Team 13 Wladimir Sougakoff

We thank the AERES board of experts for its clear evaluation of our project. We would like to bring precisions to some of the issues raised by the AERES committee.

Assessment of scientific quality and outputs

"Overall the team produces important results that translate into a insufficient high production level"

We were probably unclear in explaining that the team 13 is actually the result of the merging of two groups previously located in two distinct centres:

- Pitié Salpêtrière – EA1541/ER5 "Infection à mycobactéries (tuberculose, lèpre, mycobactériose) et antibiotiques : aspects moléculaires, thérapeutiques et épidémiologiques" (part of IFR113),

- Saint Antoine - EA 2392 "Antibiotiques et flore digestive".

The group EA2392, following AERES and UPMC recommendations (in 2008) to bridge with others Paris 6 bacteriological laboratories, began collaborating with EA1541 through teaching activities (start in 2009). Both groups extended their collaboration in 2010 by starting common research based on their common interest in antibiotic multiresistance, as illustrated by 2 recent papers (Kassis-Chikhani N *et al*. Antimicrob Agents Chemother. 2013 Jan;57(1):618-20 (IF 4.84); Drieux L *et al*. J Antimicrob Chemother. 2013 Jan;68(1):97-100 (IF 5.07)).

Actually, the publication record of the new proposed team is spread in 2 distinct parts of the CIMI report, making the reading uneasy. The number of publication in international journals is in fact 115 for ER5 and 47 for EA2392, accounting for a **total of 162 publications**.

We agree that few papers are published in broad-spectrum journals. However, the team published

1. the two papers in AJRCCM mentioned page 8 of the AERES report as high impact factor journal papers,
2. a high number of papers (n=64) in the best journals of microbiology and antibiotic resistance: J Bacteriol (2nd cited journal in microbiology), J Clin Microbiol (3rd cited journal in microbiology), Antimicrob Agents and Chemother (4th cited journal in microbiology and 1st cited journal in antimicrobial resistance), Journal of Infectious Disease (6th cited journal in microbiology) and J. Antimicrob. Chemother (8th cited journal in microbiology and 2nd cited journal in antimicrobial resistance).
3. taking into account the heavy clinical workload of some members and the lack of full-time researcher, we feel that the ratio of publications/member is not that bad (3.75 publications/researcher/year) and illustrates that team's members are hard workers.

In the future, we are confident that (i) the combination of our integration in the CIMI, (ii) the ongoing development of new projects based on innovative approaches (e.g. single particule nanomanipulation and whole-genome sequencing, with the concomitant recruitment of a foreign post-doctoral fellow) and (iii) the dynamisms of the young researchers like Nicolas Veziris who is currently in post doctoral position in Patrick Brennan's Department of Microbiology, at Colorado State University, Alexandra Aubry (present member of INSERM commission CSS7) who did her post doc in Mark's Fisher's laboratory in London and initiated a collaboration with James Berger, and Dominique Decré who did a training course in bioinformatics at the genomic platform of the Pasteur Institute and trained on the annotation software (MaGe) at the Genoscope, will allow us to publish in broader journals with higher publication level.

Assessment of the unit's academic reputation and appeal

"A few invitations to communications/participate to national/international events are reported […] Visibility at international events and attractiveness to international researchers/post-docs are not sufficient."

It is clear that our visibility at international events and attractiveness to international researchers/post-docs are not sufficient. However, we would like to underline that the dynamic strategy to attract foreign post-doctoral fellows has already begun. Indeed, an Australian post-doctoral fellow experimented in genome analysis will join our team in June 2013 for 18 months (funded by a DIM MalInf program obtained by W.Sougakoff). He will be involved in the genome-wide analysis projects that have already started based on an attentive selection of strains to be analyzed. A Peruvian PhD student will also join our team in October 2013 for one year in the context of a collaborative program France-Perou established between Dr Mirko Zimic from Peru (Universidad Peruana Cayetano Heredia) and W. Sougakoff.

Even if the number of invited conferences by members of our team is limited, we are systematically invited, thanks to our position as French National Reference Centre for mycobacteria and resistance to antimycobacterial agents, as member or speaker to European meeting (ECDC, ESCMID, WHO) on tuberculosis resistance and molecular epidemiology. One member of the team (V. Jarlier) is currently chairman of the steering committee at the European system for surveillance of antibiotic resistance organized by the ECDC (EARS.net), and has been recently nominated as expert at the European Medical Agency (London) regarding antituberculous agents. Guillaume Arlet is an international leader in resistance to beta-lactams.

Assessment of the unit's organisation and life

"The team encompasses many permanent clinical staff, all of whom may not be involved in research activity. Having less permanent staff in the team would allow recruiting more students and post-docs as well as permanent scientists. The team should seek more benefit from CIMI infrastructures and expertise."

Indeed, the team encompasses many permanent clinical staff deeply involved in clinical activities and teaching. This point is inherent in the history of the two groups that will constitute the team 13: both groups are based on clinical bacteriology staff deeply anchored in the context of their respective medical schools and hospitals (Pitie-Salpêtrière for EA1541 and St-Antoine-Tenon for EA2392). We fully agree with the major recommendation to recruit full-time researchers, but we feel that a well-balanced mix of research and clinical activities in our team is a crucial component for the development of translational research of high value, especially in the context of our activities as National Reference Centre for Mycobacteria. According to AERES recommendation, one of our team member with the lowest research activity will leave the team (Charlotte Verdet, PH), but two others members who are also PH will continue to contribute to our team. Indeed, both are PhD (since 2010 and 2012, respectively) and published well despite the fact that their time involved in research activities is only 30% (16 and 12 publications, both as first author in 4 publications in journals which mostly belong the 8 better journals of microbiology). Moreover, these permanent staff with

"heavy" clinical duties do not jeopardize student supervision, but are in fact an added value thanks to their long experience in managing supervision of juniors in clinical practice and M1/M2 students in research. Moreover, they do not take specific space in the laboratory since their time involved in research activities is only 30%.

Regarding the major recommendation to recruit full-time researchers, and in addition to the above-mentioned efforts to recruit foreign post-doctoral fellows and PhD students, the integration of the team in the CIMI will facilitate the process by the attractiveness of the CIMI consortium and improvement of the research environment.

Finally, regarding the recommendation to seek more benefit from CIMI infrastructures and expertise (e.g. animal models, immunology, etc.), we have very recently obtained an IFR113 grant to start a collaboration with Arnaud Moris's group for developing a model of assessment of M. tuberculosis virulence with a macrophage model.

Assessment of the unit's involvement in training through research

"The post graduate career of the PhD students trained by the team is difficult to evaluate, and should be better highlighted."

Most of our PhD students have found post-doctoral positions (S. Matrat who was supervised by Alexandra Aubry found post-doctoral position at Département de Santé Animale, Faculté Vétérinaire in Madrid and is currently at Unité de Microbiologie INRA Centre de Clermont Ferrand-Theix). Four of our previous PhD students have been hired as hospital practitioners (PH) in our laboratory (Florence Brossier and Laurence Drieux, theses co-supervised by Pr V. Jarlier and W. Sougakoff, Charlotte Verdet and Najiby Kassis-Chikhani, theses supervised by Pr G. Arlet). One found a leading position (equivalent to associate professor) for teaching in the university public-health staff of Haiphong medical school in Vietnam, and one as hospital practitioners (PH) in the reference team for orthopaedic infections, these two latter were supervised by Pr J. Robert.

Stephanie Petrella, who worked as postdoctoral researcher in our lab during several years, has obtained a position of associate professor (Maitre de Conference) at the Diderot University in 2011. Caroline Dallenne, who was a PhD student supervised by Pr G. Arlet is R&D Project Manager in BioRad laboratories since 3 years and E. Segala whose thesis was supervised by Wladimir Sougakoff is R&D Project Manager at Heptares Therapeutics since a few months.

Finally, it is worth mentioning that two team members are in the process to get the "Habilitation à Diriger les Recherches (HDR)" in the coming months, and therefore will be able to supervise doctoral students on their own. The total number of researchers with HDR will then reach 7.

Assessment of the five-year plan and strategy

"The project may be overambitious and should be carefully monitored […] Meetings points should be found between the two projects […] The team should be more embedded in international groups through funding agencies & international collaboration consortia"

As mentioned above, the team results from the fusion of two UMPC research units. Nevertheless, it has to be highlighted that the project of team 13 is not solely a continuation of previous activities but is also based on the development of new and innovating strategies/approaches, which accounts for the ambitious nature of our project (genome-wide analyses, structural studies, etc). This project is the result of the objective of the new team leader, as well as young researchers of the team. As suggested, we plan to carefully monitor the key strategical and technical decisions that will have to be made for the successful development of these innovating projects, in particular the choice of strains to be sequenced from our invaluable collection of clinical isolates/strains.

Regarding the recommendation to find meeting points between the two main projects of the team (i.e. MDR M. tuberculosis and MDR plasmids), two recent papers (Kassis-Chikhani N et al. Antimicrob Agents Chemother. 2013 Jan;57(1):618-20 (IF 4.84); Drieux L et al. J Antimicrob Chemother. 2013 Jan;68(1):97-100 (IF 5.07)) illustrate the active collaboration already established between the 2 groups ER5 and EA2392. In the future, the common scientific interests of the two teams (and also of other CIMI's teams!) on the impact of microbe persistence on the development of drug resistance (e.g. investigation on toxin-antitoxin systems in mycobacteria and enterobacteriaceae) should contribute to an efficient future interpenetration of the projects.

Finally, regarding the issue made by the committee that the team should be more embedded in international groups through funding agencies international collaboration consortia, we would like to highlight, as mentioned in the report, that we raised in the past an important amount of fundings thanks to industrial contacts and our position as French National Reference Centre for mycobacteria and resistance to antimycobacterial agents. We also began a more aggressive policy to attract institutional grants (e.g. we applied to ANR grants by submitting two projects "ANR blanc" in January (Full-FluoTB and STAPS) and one "ANR RPIB" in March (CliReTB : CLinical Resistant Tuberculosis). We are now convinced that the development of our team project in the context of the CIMI centre, will foster the international impact and visibility of our researches and will promote our international attractiveness and capacity to respond to calls from international collaboration consortia and funding agencies.

Team 14 Vincent Vieillard

We thank the committee for this very positive comment.