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

Department for the evaluation of research units

AERES report on unit:

Immunology of Infectious and Autoimmune Diseases

ImVad

Under the supervision of the following institutions and research bodies:

Université Paris-Sud

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

Commissariat à l'Énergie Atomique et aux Énergies Alternatives - CEA

December 2013

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

Department for the evaluation of research units

On behalf of AERES, pursuant to the Decree of 3 november 2006[1]*,*

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

On behalf of the expert committee,

– Ms Jacqueline MARVEL, chair of the committee

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

Evaluation report

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

Unit name:	Immunology of Infectious and Autoimmune Diseases
Unit acronym:	ImVad
Label requested:	Université Paris-Sud, Inserm, CEA
Present no.:	Fusion UMR S-1012 and UMR E1
Name of Director (2013-2014):	Mr Marc TARDIEU (UMR S-1012) and Mr Roger LE GRAND (UMR E1)
Name of Project Leader (2015-2019):	Mr Roger LE GRAND

Expert committee members

Chair:	Ms Jacqueline MARVEL, Inserm Lyon
Experts:	Mr Henri AGUT, Université Pierre et Marie Curie, Paris
	Ms Béhazine COMBADIÈRE, Center of Immunology and Infectious Diseases, Paris
	Ms Monique LOMBARDY-ALRIC, Université de Clermont-Ferrand (representative of CNU)
	Mr Manuel ROSA-CALATRAVA, Université de Lyon (representative of CSS Inserm)
	Mr Benoît SALOMON, Center of Immunology and Infectious Diseases, Paris

Scientific delegate representing the AERES:

Mr Joost VAN MEERWIJK

Representatives of the unit's supervising institutions and bodies:

Mr Etienne AUGE, Université Paris-Sud

Mr Karl BALABANIAN (representative of Doctoral School n° 425)

Mr Gilles BLOCH, CEA

Ms Laurence PARMANTIER, Inserm

1 • Introduction

History and geographical location of the unit

The new Research Center "Immunology of viral infections and autoimmune disease" will be formed by the merger of two research units; the UMR-E1 Immuno-virology unit and the Inserm unit 1012 (Regulation of the immune response to HIV infection and Autoimmunity).

The UMR-E1 Immuno-virology unit (UMR-E1 unit hereafter) is part of the IMETI (institute of emerging diseases and innovative therapies) of the CEA. It was restructured in 2007. The unit is located on the CEA campus in Fontenay-aux-Roses which is exclusively dedicated to life sciences and biomedical research. This UMR will become team 4 of the proposed Research center.

The Inserm unit 1012 (U1012 here after) is located on the Université Paris-Sud medical campus that includes the Kremlin-Bicêtre hospital and medical school. It was created for the 2010-2014 period by the Inserm and the Université Paris-Sud. The three research groups of this unit will become teams 1, 2, and 3 of the proposed center.

The teams belonging to the two units will remain on their respective sites, which are 20 minutes distant by car (10km/40 minutes by public transport).

Management team

The center will be managed by its director with the help of a steering committee that will be composed of the team leaders and the coordinator of the Support unit/technical facility (IDMIT). The steering committee will be in charge of organising the center's administration, budget and resource allocation, it will define its scientific strategy and manage the center's interaction with the IDMIT platform. For its scientific strategy the center will rely on a scientific advisory board constituted by international experts in the field of infectiology.

The present UMR-E1 unit is subdivided in two scientific departments and one support team, all under the direction of the director. The laboratory of antiviral immunity is headed by the unit's director and is aiming at developing research programs on host-virus interactions. Different topics are studied each being led by a senior scientist. The second scientific department, headed by a senior scientist, is focussed on technological research and developments in the field of immunomonitoring of the immune response of non-human-primates (NHP) following viral infection or vaccinal challenge. This department regroups all the unit's technical resources, equipments, and core facilities. It is involved in a large number of collaborative programs and has obtained PIA ("programme investissement d'avenir") grants to reinforce its core facilities. The support team is running the unit's budget and contracts, is giving support for grant applications, and is working on the implementation of a new infrastructure (IDMIT) financed by the PIA.

The present U 1012 was created with a staff of 30 members dedicated to perform multidisciplinary clinical and basic research in the field of immunology applied to infectious diseases, mainly HIV, and autoimmune disorders. The U 1012 is organised around three major scientific questions without formal teams to maximize interactions. The director and a part-time secretary are in charge of financial and administrative matters. The funding obtained from Inserm is used to improve technical platforms (50 %), cover general expenses (40 %), and promote emerging projects (10 %). The whole unit meets once a week for a seminar (internal or invited speaker). Topic-specific meetings are held generally once a week, with involved lab members. The scientific strategy is defined by the permanent scientists.

AERES nomenclature

SVE1_LS6 Immunology, microbiology, virology, parasitology

SVE1_LS4 Physiology, physiopathology, medical systems biology

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	5	16
N2: Permanent researchers from Institutions and similar positions	20	21
N3: Other permanent staff (without research duties)	19	22
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	12	11
N6: Other contractual staff (without research duties)	10	3
TOTAL N1 to N6	**66**	**73**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	13	
Theses defended	12	
Postdoctoral students having spent at least 12 months in the unit*		
Number of Research Supervisor Qualifications (HDR) taken	4	
Qualified research supervisors (with an HDR) or similar positions	13	18

2 • Overall assessment of the unit

The UMR-E1 unit has developed a unique knowhow in NHP models for infectious disease and vaccinal challenge. It is involved in a large number of collaborative programs and is supporting through these collaborations high quality research. The technological expertise of the unit and its recognition within the community has allowed it to gain several grants within the PIA that are used to purchase new equipment to develop top notch technologies and expand the technical facilities associated with the unit. Hence this unit and the associated platforms represent a unique asset for French and international research in infectiology and vaccinology.

The U 1012 is involved in multidisciplinary clinical research; clinicians with a diversity of expertise are involved in the unit (Infectiology, Internal medicine, Rheumatology, clinical Haematology, Paediatric Neurology). The unit performs mainly clinical research. This is facilitated by the strong clinical anchorage of its senior members who are all clinicians but also by their longstanding involvement in the setup of human cohorts. The team is managing several of them and is using them to develop its clinical research. In parallel it performs translational research towards industry and the clinic via the development of new assays or biomarkers for the diseases they are studying and the setting up of new therapeutics approaches. It also performs translational research by developing preclinical pathophysiological models of human diseases to test new hypotheses that are drawn based on the results of its clinical research. Overall, this multidisciplinary clinical research unit is producing innovative research of an excellent quality.

Strengths and opportunities related to the context

The expertise of the present UMR-E1 lies in the development of NHP models of human infectious diseases and cutting edge assays to follow the NHP immune response *ex vivo* or *in situ*. PIA programs that have allowed the acquisition of top-notch technologies for single cell phenotyping (i.e. Cytof) have reinforced these existing strengths. The animal facility and associated research labs will be redeveloped thanks to the IDMIT's PIA grant. Finally, the UMR-E1 is part of the "laboratoire d'excellence" VRI (Vaccine Research Institute) which leads to fruitful collaboration and co-developments.

The clinical research carried out by the present U 1012 represents an asset for the future center. The different patient cohorts (HIV, Sjögren's syndrome, rheumatoid arthritis, spondyloarthritis) that it is coordinating will allow it to continue on this excellent clinical research track.

Both units are involved in translational research with a good network of contacts with industry.

The fusion of the two units into a new research center should lead to the development of new NHP models of disease that will form a continuum allowing the reciprocal translation between clinical and experimental research.

The global approaches (multiparametric-phenotyping, transcriptomics) that are currently developed by the UMR-E1 to analyse data in NHP models will represent an asset as they could easily be applied to clinical samples.

Weaknesses and threats related to the context

Despite the existence of common research programs, most of the clinical researchers of the former INSERM U 1012 (who are working at the Bicêtre Hospital site) so far have a limited involvement in the experiments conducted at the CEA's platform and technological research facilities. Due to the geographical distance between the CEA campus in Fontenay-aux-Roses and the Bicêtre hospital site and the different ethos of the two units, the development of these links will require a positive reinforcement in terms of management and coordination.

The physical distance between the two sites could also represent a problem for e.g. students.

The multidisciplinarity of the clinical teams could be a weak point in these new settings, as the likelihood of fostering links with the CEA platforms is not the same for all teams.

Recommendations

Due to the geographical distance between the two sites on which the to be fused units are located, the organisation of the future center's life will have to take into account the constraints associated with the different categories of team members (clinicians, students, technicians etc.) and make sure that all have the possibility to be involved in the center's scientific life and meetings.

The CEA could recruit a new team devoted to infectiology studies in NHP.

The two units had different policies in terms of technical-staff association with teams. These made sense in the previous settings of the respective units. However, the new center should establish a clear policy that is uniform and takes into account the needs of the structure as a whole but also of the teams.

The "territory" of the center should be clarified as the overlap between the center and the PIA platforms was perceived differently by the different actors we met: unit directors, team heads, unit members, or institution representatives. A clear communication on that subject within the center but also towards the institutions and PIA-platform partners is recommended.

3 • Detailed assessments

Assessment of scientific quality and outputs

The two units have an excellent publication output. The U 1012 published more than 300 papers, with 17 in journals with an impact factors above 10 and 71 in speciality journals with an impact factor between 7 and 10. Only a fraction (±20 %) of these papers has a unit member as senior author. The majority of the publications are from collaborations involving unit members, reflecting their strong involvement within their scientific field. The unit has access to a large number of cohorts, some of which are coordinated by members of the unit (HIV patients (HIV Primo cohort, IPERGAY, ANRS CO16 Primovac), Sjögren's syndrome patients (ASSES cohort), rheumatoid arthritis patients (ESPOIR cohort), spondyloarthritis patients (DESIR cohort), EBV infection and lymphoproliferative disorders patients (Lymphovir cohort)). It is also involved in a significant number (n=10) of clinical trials. Overall this is an excellent research output for a unit of a relatively small size.

The UMR-E1 unit's output results from different activities. First, the running of the NHP platform dedicated to infectiology-vaccinology, and the associated technological team that is involved in the development of assays to monitor the NHP immune response, have led to numerous collaborative projects, many of them at the international level. These collaborations have led to a large number of publications that are co-signed by UMR-E1 unit members, reflecting their involvement in the research. Some of technological developments (e.g. data-bases) have been licenced to other labs (academic or industrial). Second, the research team is developing its own research mainly on primary infection by HIV. This research on NHP has led to important discoveries on the initial host-immune response following HIV infection and on therapeutic approaches that could limit infection. Overall, the unit has published 64 papers, 12 of them in journals with an impact factor above 10. This is a very good output for the unit and associated platform-members.

Assessment of the unit's academic reputation and appeal

The two units are both renowned for their involvement in HIV research; the UMR-E1 unit for its HIV-NHP models and the U 1012 for its involvement in studying multiple HIV cohorts. The head of the ANRS is member of the U 1012, he has an international aura for his scientific but also social involvement in the fight against HIV. The group working on auto-immune diseases is also highly recognised by its peers, as illustrated by its involvement in international networks, invited reviews in prestigious journals, etc. This excellent level of recognition represents an appeal force for the center.

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

Both units are strongly involved in multiple aspects of the social and economic environment. They both have fostered links with industrial partners, via the NHP platform (Bertin Pharma), and through the licencing of patents or obtaining research grants. Their success with the PIA calls (equipex and infrasture) will extend the UMR-E1 platform's capacity and the technologies offered. This will reinforce their existing, highly recognised, role in the structuration of the research community working in immuno-infectiology in NHP. Finally, the clinical research performed in the U 1012 and involvement of team members in different patient cohorts, networks, or funding bodies have a far-reaching impact on patients and social environment.

Assessment of the unit's organisation and life

The two present units have a different organisation scheme that was justified by the type of research activities they were performing. The two groups were relatively small in size (around 40 members), allowing for an apparent good communication within each unit. However, neither unit has a laboratory board ("conseil de laboratoire") in which all categories of staff were represented. This type of structure will be necessary in the new center. The distribution of technical staff between platforms and teams will have to be revised taking into account the needs of the center but also of the teams. Currently, the two units have regular meetings to manage the lab or discuss scientific matters, this organisation seemed satisfactory. However, in the future center, due to the geographical distance between the two sites, the organisation will have to take into account the constraints associated with the different categories of team members (clinicians, students, technicians, etc.) and make sure that all have the possibility to be involved in the unit's scientific life and meetings.

Assessment of the unit's involvement in training through research

Both units are involved in or are running Master courses. They have also trained a significant number of Master and PhD students. The relationship with the Doctoral School ("École Doctorale") is excellent; no problems have been encountered in the past 4 years. Most students have papers signed as first authors. On average, PhD-theses are defended within four years, which is in accordance with the doctoral school practice. The training provided by the units to PhD students and the involvement in teaching is diversified (Master courses, Medical training, PhD training). Overall, the units' involvement in training PhD students is of an excellent level.

Assessment of the strategy and the five-year plan

The new ImVad center will be composed of four teams that will be associated with the NHP and technological platforms. Team 1 will focus on chronic viral infections, mainly HIV and SIV. Research will be performed in the clinic and in NHP models. Team 2 will use mouse models to study the role of CD4 T cell subsets in the generation and maintenance of functional memory CD8 T cells. It will also perform translational research to define the role of memory CD8 T cell-defects in the development of chronic viral infections. Team 3 will study the mechanisms involved in the development of systemic autoimmune diseases, such as primary Sjögren's syndrome, using clinical research and mouse models. It will develop an original model of rheumatoid arthritis in NHP. Team 4 will focus on anti-viral immunity and will try to define correlates of protection for these pathologies or vaccines targeting them.

The new center will have three transversal aims:

- first, "the definition of molecular and cellular mechanisms underlying the generation and regulation of immune memory and tolerance";

- second, "the comparison of the impact of inflammation on immune effectors in chronic viral infections and autoimmune diseases";

- third, "the identification of biomarkers of the safety and efficacy of treatments modulating inflammation in chronic viral infection and autoimmune diseases".

These are really long-term, very ambitious aims and it was not always clear how each team will contribute to them. The fulfilment of these aims will also depend on ongoing collaboration with teams within the Labex VRI and the "Centre National de Génomique" (CNG) for modelling, genomics, and bioinformatics expertise.

The platforms associated with the ImVad center will develop technological research to setup multiparametric single cell phenotyping, *in vivo* imaging, and mathematical modelling of data. Their aims in terms of innovation are:

1) the identification of new biomarkers;

2) the development of new technologies and methods for monitoring disease status;

3) the identification of targets for the development of new drugs;

4) the development of new therapeutic approaches.

Overall, the center will build on the existing expertise with an aim to synergize activities between the four teams and the platforms and broadly collaborate when the expertise is not present within the participating teams. This seems a good strategy. However, this set-up will involve multiple interactions that could become a burden from a managerial point of view for teams with a limited number of full-time scientists. Although the project is globally very good, the tools and platforms available could support more innovative research using NHP models. They should be used to attract a new team or new permanent scientists that could reinforce some of the teams with limited numbers of full-time scientists.

The organisation of the ImVad center was discussed during the on-site visit. The distribution of staff between the center and the associated platforms was not clear from the written document. The director presented an organigram. Discussions have highlighted that the structuration of the ImVad center and its relation with the PIA platform IDMIT is still under discussion. Once finalised the overall organisation of the center and its articulation with IDMIT should be shared with the center's staff.

4 • Team-by-team analysis

Team 1: Control of Chronic Viral Infections

Name of team leader: Mr Olivier LAMBOTTE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		6
N2: Permanent EPST or EPIC researchers and similar positions		5
N3: Other permanent staff (without research duties)		3
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		2
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6		**16**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		9

• Detailed assessments

Assessment of scientific quality and outputs

The output and scientific quality of this U 1012 research group, which will become team 1 of the proposed center, is emblematic of the activity of Inserm U 1012: translational research based on a strong clinical interface, major interest in the regulation of human immune response against infections, close interactions with Paris-Sud Faculty of Medicine and national research networks. This has led to innovative results, mainly in the field of HIV infection, some of them being considered as major breakthroughs in this domain. The most prominent data concerned

the control of HIV replication at early stages of infection, particularly in a small subset of HIV-infected subjects designated as HIV controllers. As the principal investigator of ANRS controller cohort, the contribution of the head of the group to the HIV field is exceptional.

Under the auspices of ANRS and thanks to an efficient national clinical network, which provided a wide access to cohorts and samples, the virological and immune characteristics of these subjects have been investigated, leading to the conclusion that this subpopulation is heterogeneous, albeit exhibiting a common capacity to spontaneously control HIV replication. This topic has been extended to the question of HIV latency and T cell reservoirs. More basic questions have concerned T cell depletion induced by HIV and its impact on regulation of immune responses, particularly on Treg populations, IL-7 bioavailability, and lymphocyte interactions in intestinal mucosa. Papers reporting the results of the team have been published in high quality international journals, albeit not top rank generalist ones, such as PLoS Pathog, PloS One, JID, AIDS, J Immunol, CID, which represent a very good level of dissemination in the competitive context of HIV research.

Assessment of the team's academic reputation and appeal

The group has a well-established national academic reputation. Its leader is the Principal Investigator of the ANRS CO18 HIV Controller cohort study, which involves ten research teams in France and the USA. He has an international visibility as a member of collaborative research networks on HIV controllers, organizer of a symposium on HIV controllers at the AIDS Vaccine Congress in 2009, and presenter of an oral communication at Keystone Meeting 2013. As a specialist of Internal Medicine and Clinical Immunology, the leader is also involved in research works concerning other fields than HIV infection and appears as a co-author of high input publications in internal medicine and haematology. The current head of ANRS agency is a member of the group.

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

The group occupies a prominent position at Bicêtre Hospital and Faculty of Medicine of Université Paris-Sud. In terms of technical support, the group has developed full access to BSL2 facilities and equipment dedicated to immunological, cellular and genetic analyses. It also takes advantage of close interactions with the laboratory of immunology, the clinical investigation center, and the epidemiology center of Bicêtre Hospital and Université Paris-Sud as well as with leading teams in Institut Pasteur. In terms of translational research, patent deposit and relationship with non-academic partners, the contribution of the group is more limited.

Assessment of the team's organisation and life

The group is constituted of ten members, some of them having important clinical and teaching duties: 3 PU-PH (university professors and clinical physicians), 1 PH (clinical physician), 2 full-time researchers (1 CR, 1 DR), 1 post-doc, 2 PhD students, 1 engineer (temporary position). The group as a whole participates to weekly seminars, which gather all the staff of the research unit. This point could be reinforced.

Assessment of the team's involvement in training through research

The leader of the group is the director of the Immunology Master course at Université Paris-Sud and the group is affiliated to the Doctoral School "Innovation Thérapeutique" of Université Paris-Sud. Two PhD students are currently members of the staff. Due to the proximity with hospital staff, the training of physicians to research activity by the group must occur, especially for clinically oriented research. Overall, the participation of the team in training through research is good.

Assessment of the strategy and the five-year plan

The project of team 1 for the next five years is proposed in the context of the creation of the research center on immunology of chronic viral infections and autoimmune diseases, resulting from the merger between Inserm U 1012 and UMR-E1. This creation offers the opportunity to develop ambitious transversal programs in immunology and infectious diseases, from bench to bedside and vice-versa, with the general goal of improving the understanding of pathophysiology processes and providing novel rationales for the treatment of chronic viral infections. Fitting those objectives, team 1's program will remain dedicated to the study of mechanisms supporting the control of chronic viral infections, with a specific emphasis on HIV infection and its simian counterpart, SIV infection in a macaque model. With some members of UMR-E1 joining the team, it will offer the opportunity to develop translational NHP

programmes on the role of innate immunity (plasmacytoid and myeloid dendritic cells, secretion of interferon) in the early control of HIV/SIV infection. The capability to conduct studies in parallel both in HIV-infected subjects and SIV-infected macaques can be considered as a major asset.

The second axis is the study of viral persistence mechanisms in chronic HIV/SIV infection focusing on the role of fat tissues as a reservoir, and the links between the reservoirs and HIV-specific CD8 and CD4 T-cell responses. The rationale for considering adipose tissue as a major parameter for HIV persistence is not truly justified. In addition, the study of this body compartment in humans may be complex and has to face much more technical restrictions than in macaque or mouse models. Therefore this part of the project, albeit innovative, is to be considered high-risk and needs to be monitored very carefully.

The third aim is the continuation of the research program on HIV controllers and the attempt to decipher the parameters of viral control in SIV-controller macaques, in particular the recognition of protective MHC alleles. This part of the program appears conventional but perfectly fits the previous experience and success of team 1 and its co-workers, supported by a fully efficient collaborative network.

Conclusion

- **Strengths and opportunities:**

Unique opportunity to link investigations on HIV infection in humans and SIV infection in macaques.

Complementary skills and technical approaches, providing a wide range of investigations from clinical approaches to laboratory and animal studies.

Perfect fit between team 1's research program and the general scope of the new center.

Density of the collaborative network, both at national and international levels.

- **Weaknesses and threats:**

Location of the team on two distinct sites, which may affect the ideal theoretical complementarity between members of the team and appeal for students and young researchers.

Lack of a clearly defined recruitment policy for future staff, the current one being limited in number and mainly constituted of scientists having weighty clinical and teaching positions.

In view of the previous achievements of the team and despite the relevance of the current project, the program seems rather conventional, except for the second aim, more innovative but high-risk. Contingency plans need to be proposed.

Currently, the team's funding is essentially obtained from the French agency for HIV research, ANRS. Funding applications should be extended to other sources, either academic (e.g. EU and NIH) or non-academic (pharmaceutical firms).

- **Recommendations:**

Clear policy for the identification and recruitment of young researchers in the future.

Diversification of funding sources.

Clarification of interactions between clinical and academic research in the context of the novel center, these interactions being the major asset and the driving force for the development of the team.

Team 2: Normal and Pathological T cell-Memory

Name of team leader: Mr Yassine TAOUFIK

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		4
N2: Permanent EPST or EPIC researchers and similar positions		1
N3: Other permanent staff (without research duties)		4
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		3
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6		**12**

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

• Detailed assessments

Assessment of scientific quality and outputs

The research group "Normal and Pathological T Cell Memory" of the present U1012, which will become team 2 of the proposed center, is studying the role of CD8 and CD4 T cells with a focus on memory cells to dissect basic mechanisms in mouse models and in different pathologies associated with chronic viral infections. It performs clinical research at a high level, which is associated with the development of fundamental research on in vivo models and the development of diagnostic assays based on its clinical discoveries. In the past 5 years it has published more than 20 papers among which one Nature Communication, two J. Immunol, one JID, two Blood and four PLoS One. Its main contributions are the demonstration that Treg CD4 cells are essential for the generation of efficient memory CD8 T cells; the demonstration, in a clinical trial, that CD4 T cell recovery can be accelerated by IL-7 treatment of PML (progressive multifocal leukoencephalopathy) patients following antiretroviral treatment; the demonstration that memory T cells specific to JC virus are increased in multiple sclerosis patients treated with Natalizumab (anti-VLA4

antibody). This is an excellent scientific output. The group's research has also led to a patent for an assay that detects memory T cells specific to JC virus. The research is highly translational and, in the field of human memory T cell-development, innovative. The group is well connected at the international level since it has European and American collaborators.

Assessment of the team's academic reputation and appeal

The group is responsible for several cohorts of patients (HIV Primo cohort (ANRS C06), Lymphovir (ANRS CO16), Paediatric hepatic transplant cohort, LH-EPI cohort, PML cohorts) that are used for clinical research by a number of teams. It is part of two international networks: the PML-17 network and the latent reservoir network. The group has obtained funding from ANRS and from several industrial partners. This high level of collaborations and research management represents an appealing asset for clinical researchers.

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

The group has strong links with industrial partners and, based on its gained knowledge, is developing assays to monitor disease progression and for diagnostics. Its clinical research should also lead to the development of new therapeutic strategies or the improvement of existing treatments for patients (HIV, PML). One assay developed by the group has indeed been patented and is currently licenced.

Assessment of the team's organisation and life

The group is composed of four clinicians (2 MCU/PH, 1 PU/PH and 1 PH), two PhD students, one post-doctoral fellow and five engineers and technicians (1 tech, 1 AI, 2 IE and 1IR). It is organised in five sub-groups working on specific scientific questions, each member belonging to more than one sub-group. The group was previously part of a single-team unit (U1012) and as such was participating in the unit's meetings as a subgroup. The future organisation of the team in terms of e.g. lab meetings etc. was not detailed in the project. However this team will mainly work on the hospital site, hence they will have an easier job in terms of team life and organisation.

Assessment of the team's involvement in training through research

The group is currently training two PhD students and is involved in Master courses. This number of students represents a good student to team-size ratio. Based on the information given, this represents a fair involvement in training through research.

Assessment of the strategy and the five-year plan

The team research proposal follows on its previous discovery and will develop three topics.

The first one will address the role of CD4 T cells in the generation and persistence of memory CD8 T cells. The team will study the role of TFH (Follicular CD4 Helper cells) in the generation of efficient memory CD8 T cells. It will address this question in genetically modified mouse models that allow the specific abrogation of subsets of CD4 T cells. It will also study the role of a new subset of CD4 T cells, which can recirculate between peripheral tissue and secondary lymphoid tissues, in the persistence of tissue resident memory CD8 T cells. This is an innovative project that addresses important new questions in the field of memory CD8 T cells. Although the questions addressed are innovative and important, the rational and the experimental approaches that will be used are not always clear or well justified. A better focus on a restricted number of questions is advised.

The second topic corresponds to clinical research on different pathologies that are associated with a defect in T cell responses due to chronic viral infection. The team will study if early (prophylactic or during primary infection) treatment of HIV patients with anti-retroviral therapy (ART) impacts on the quality of HIV specific CD8 T cells. The underlying rational is that decreasing the virus load at an early stage in the infection might allow the generation of CD8 T cells that are able to control the virus in the absence of antiviral drugs. The team will continue its clinical trial on PML patients (HIV and MS). The goal here will first be to define the best clinical protocol to restore T-cell-based immune surveillance of the JC virus, second to develop new diagnostic tools to predict PML development in MS patients treated with natalizumab, and third to identify genetic variants among MS patients that are associated with a predisposition to PML development. Finally the team will monitor CD8 T cell functionality in paediatric patients with a liver transplant that are at risk of EBV infection and assess the impact on lowering tacrolimus immuno-suppressive treatment.

The third topic will focus on the identification of the CD4 subset that is an HIV reservoir in long term ART patient with undetectable plasma virus. The TRCM subset that traffics between tissue and blood will be more specifically studied. The imaging of this subset of CD4 T cells will be performed in NHP at the CEA facility. This study on a new subset of CD4 T cells is a follow-up of previously published work defining subsets of CD4 cells that act as a reservoir for HIV.

This clinical research project based on existing cohorts that are managed by team members is ambitious, feasible and innovative. The assays that will be performed are mastered by the team. Moreover, the team has already obtained funding for these projects.

Conclusion

- **Strengths and opportunities**:

Excellent clinical research and translational research. Strong links with industrial partners. Access to cohorts that allow an in-depth analysis of immune defects in human.

- **Weaknesses and threats:**

The research team is, considering the number of subgroups and hence research topics (n=5), relatively small and a full time researcher is lacking. The rational of some parts of the project (i.e. studies in genetically modified mice and cell reservoirs of HIV patients on long-term ART treatment) was not very convincing.

- **Recommendation:**

The links with the NHP models and the collaboration with the CEA team should be strengthened.

Team 3: New Mechanisms Involved in Pathogenesis of Autoimmune Diseases

Name of team leader: Mr Xavier MARIETTE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		6
N2: Permanent EPST or EPIC researchers and similar positions		2
N3: Other permanent staff (without research duties)		1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		2
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6		**11**

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

- ## Detailed assessments

Assessment of scientific quality and outputs

Most of the members of this U1012 research group, which will become team 3 of the new center, are part of the Rheumatology, clinical Haematology or Paediatric Neurology Departments at Bicêtre Hospital. Through these departments, active networking, responsibilities in various national registries (i.e. Reference Center for Inflammatory Diseases of the Brain) and through external collaborations, the group has access to biological samples from large cohorts of patients (400 to 800) who have Sjögren's syndrome, rheumatoid arthritis or spondyloarthritis. What is remarkable is the global approach to study Sjögren's syndrome going from human genetics to sample collections in order to assess the role of inflammatory factors and pathogenic cells such as B or NK cells. The group was among the first to reveal an interferon signature in Sjögren's syndrome. It proposes to study Sjögren's syndrome as a model of a systemic autoimmune disease for several major reasons:

(I) the prevalence of the disease is relatively high for an autoimmune disease;

(II) the group has access to a large number of samples from the main target organ, the salivary glands, because of regular biopsies;

(III) it is the autoimmune disease most frequently associated with lymphoma (5 % of patients).

The group showed that accumulation of NK cells within salivary glands is associated with poor prognostic. It described mutations in A20 that regulate NF-kB, which was associated with lymphoma. It has also studied patients with lymphoma associated with HIV and HCV infections. Comparing the pathophysiology of Sjögren's syndrome-associated lymphoma and viral-associated lymphoma may generate original and important findings. The study of Sjögren's syndrome has a high impact since it significantly improved our understanding of the pathophysiology of systemic autoimmune diseases. In addition, the part of the group specialized in neurologic sciences had provided significant results in the field of demyelinating diseases and encephalitis in children.

Since 2008, group members signed as first or last authors on more than 30 papers in the field of clinical research. Many of them are published in high to very high standard journals, such as Lancet Neurology, Lancet Oncology, Nature Review Neurology, Ann Rheum Dis, Ann Neurol, Arthritis Rheum, and Neurology.

As a whole, based both on the high quality of the results and the relevance of its translational research, the scientific output of the group is very good.

Assessment of the team's academic reputation and appeal

The group is well known in the field of autoimmune diseases and is internationally recognized for the study of Sjögren's syndrome or paediatric multiple sclerosis. The group's leader is on the Editorial Board of Ann Rheum Dis, the leading journal in rheumatology. He has served for two years as president of the scientific committee of the European Society for Rheumatology (EULAR). The group obtained three main grants during the 2010-2013 period, from the "Agence National de Recherche" (ANR Blanc 2010), Pfizer (2011) and Roche (2011). These last two sources of funding highlight the team's close connections with pharmaceutical companies. Team members coordinate two large collections of patients with Sjögren's syndrome from 15 French centers. A member of the team was the former head of Inserm research unit U 1012 and member of several national and international steering committees on research about paediatric neurologic diseases. Thus, the team is well recognized among its peers and has demonstrated its full capability for networking in the context of its research program.

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

Most group members are clinicians or medical biologists in Bicêtre Hospital. They are strongly involved in translational research and are involved in several clinical trials. They have connections with pharmaceutical companies.

The group-leader is the Head of the Rheumatology Department, and two other group-members are the head of the Clinical Haematology and the Paediatric Neurology Departments.

The group-leader is responsible for various national registries relating to biological treatments for autoimmune diseases. He has also a central role in a national association (Club Rhumatismes et Inflammation) that is very efficient in organizing meetings and a website to inform clinicians of the most recent findings in chronic inflammatory systemic diseases.

A member of the group is the Head of the National Reference Center for Inflammatory Diseases of the Brain, an elected member of the steering committee of the International Paediatric MS Study Group and Head of its Clinical Trials Task Force. The group has established the major prognostic factors for paediatric multiple sclerosis and the principal differential diagnoses. Its members are leaders in the establishment of clinical trials in children, working in close connection with pharmaceutical companies. In summary, the research activity of the group has a direct impact on the management of autoimmune diseases, which are a major burden in human morbidity. It reflects a complete adequacy with medical and social priorities.

Assessment of the team's organisation and life

The group was part of Inserm U1012 located at the Faculty of Medicine of Université Paris-Sud, within the campus of Bicetre Hospital. Its activity is fully and successfully entangled with that of the hospital and the Medical Faculty, in the context of translational research. The future organisation of the group in terms of e.g. lab meetings was not detailed in the project, hence it cannot be assessed. In parallel with the deep involvement in the management of research on autoimmune diseases, it is recommended that the project of internal scientific formation and information would appear more clearly in the overall program of the team.

Assessment of the team's involvement in training through research

One PhD student is currently member of the staff but the overall number of students trained in the group during the last five-year period needs to be precisely quantified. The participation of training physicians to research activity of the group, especially for clinically oriented research, if present, should be described and quantitatively evaluated.

Assessment of the strategy and five-year plan

The project will be performed in continuation of results obtained by the group but with new questions, models and approaches. Using collections of samples obtained from large cohorts of patients with systemic autoimmune diseases and chronic viral diseases (see above), the members of the team will study:

(I) the genetics and epigenetics;

(II) the role of NK and B cells;

(III) the mechanisms of lymphomagenesis in these diseases. They will also try to establish a new model of rheumatoid arthritis in macaques.

The originality of the project is excellent. Some of the scientific questions that the team will address are pioneering. For example, the team will explore whether the IFN signature described in Sjögren's syndrome is related to deregulation of endogenous retrotransposons in salivary glands. It will also study X chromosome inactivation in triple X women who develop an autoimmune disease. From patient samples and animal models, it will have a unique opportunity to study the role of NF-¤B in lymphomas associated with systemic autoimmune diseases and compare it to lymphoma associated with HCV infection.

The feasibility of the project is excellent. The team has access to large collections of samples from patients. It has strong expertise in the study of genetics and NK and B cells in autoimmune diseases as well as lymphomas in humans. Epigenetic-studies will be performed with cutting-edge collaborators of the "Centre National de Génotypage" at Evry. The team will take advantage of the new research unit and close collaboration with the IDMIT facility to set up a new model of rheumatoid arthritis in macaque based on immunization with citrullinated peptides that should be more relevant than classical mouse models. This project is risky but worth trying because it could help to explore new routes for the treatment of this frequent debilitating human disease.

Conclusion

- **Strengths and opportunities:**

The major strength of this team is the translational research performed to analyse the pathophysiology of systemic autoimmune diseases and lymphoma associated with these diseases or HCV infection. It has access to large cohorts of patients. Some of the questions raised in the project are cutting-edge.

The team has a global approach to analyse the pathophysiology of Sjögren's syndrome with a strong expertise in genetics, histology of salivary glands, cellular immunology (NK cells and B cells), and molecular immunology (NK receptors, B cell activation factors).

Clinical research studies performed in humans will be strengthened with studies performed in mouse and macaque models using the IDMIT facility.

- **Weaknesses and threats:**

Funding may be an issue in the future.

Currently there are only two full time researchers in the team (1 PhD and 1 PostDoc). This could be an issue for the study of animal models, which required a substantial amount of manpower and time.

- **Recommendations:**

Increase the number of full-time researchers in the team.

Diversify funding sources.

Team 4: Viral Transmission, Antiviral Immunity, and Vaccines

Name of team leader: Mr Roger LE GRAND

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	
N2: Permanent EPST or EPIC researchers and similar positions	14	13
N3: Other permanent staff (without research duties)	12	14
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	12	4
N6: Other contractual staff (without research duties)	4	3
TOTAL N1 to N6	**43**	**34**

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

• Detailed assessments

Assessment of scientific quality and outputs

The program of the UMR-E1 (which will become team 4 of the new research center) is focused on virus/host interactions in NHP. The use of NHP models is of importance and considered to be a unique opportunity to conduct on HIV/SIV infection in viral transmission and pathogenesis. The originality of the scope of the conducted research is good and relevant to the field of infectious diseases for innovation of therapies. Indeed, the team contributed to the understanding of the cervico-vaginal transmission of SIV/HIV and the identification of correlates of protection in mucosal challenge studies. The publication record of the team is very good in the competitive context of HIV research (PLoS Pathol, Blood, AIDS, PloS One). In addition, the development of other viral infection models in NHP is of importance for the future, such as Chikungunya and influenza infection.

The major success of the team is its major contribution in methodological and technical techniques adapted for NHP. It opens an excellent opportunity to investigate mechanism of infection or vaccination in NHP at national and international levels and through an extensive collaborative network of the team leader. The contribution of the team and its leader to the field is excellent.

Assessment of the team's academic reputation and appeal

The team is regarded nationally and internationally and has a sustained record of accomplishments that places it among the most valuable collaborators on NHP studies in the field of HIV. The lab has excellent visibility nationally and at the European level. The reputation of the leader is excellent with good record of publications.

The team is coordinating the Flow Cytech Equipex for the implementation of Cytof, is a partner of VRI (Vaccine Research Institute Labex), and is the founder of the recently created IDMIT infra-structure (infectious disease models and innovative therapies). Its lead in partnership and scientific involvement in international and national projects to conduct extensive programs on NHP models of various infectious diseases is exemplified by its multiplicity of partners and networks. The number of foreign post-doc is limited and could be reinforced.

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

The reputation and visibility of the team leader and his interaction with the social, economic and cultural environment is a major strength. The team leader is also the head of the IDMIT platform and has built a strong partnership with private companies through this platform. Technical innovations and products are potential outputs of the program that could be patented and transferred to the therapies market. The impact of partnership on the emergence of new research programs for the unit is very good.

The construction of the IDMIT infrastructure is an excellent indicator of transferred knowledge and technical approaches from the team to the platform, as assessed by the members of IDMIT infrastructure who have been trained in the unit.

Assessment of the team's organisation and life

The team is extremely well funded and has integrated programs in VRI-labex, ANRS, CEA, and Inserm and also benefits from large EU funding, assessing the networking capacity of its leader and the interest in NHP and CEA infrastructure to promote large-scale programmes. The team leader, who also leads the IDMIT infrastructure, allows the team to benefit of a well-organised platform to exchange knowledge and technologies among the team members.

Junior and senior researchers have also joined the team recently attesting of the attractiveness of the team. However, risk-taking responsibility assumed by the experienced researchers in the construction of multi-disciplinary projects is low.

Communication between the team leader and staff (researchers, students, post-doc), their representation on steering committees, and collegiality of decisions need to be reinforced.

Assessment of the team's involvement in training through research

The team is involved in training programs of Université Paris-Sud and others at the national and international level.

Assessment of the strategy and the five-year plan

The general objective of the programme is to provide a new scientific rational for the development of approaches to prevent viral transmission and disease. The project aims at identifying biomarkers of protection against infections and for innovative vaccine development. The leader will need to focus on the translation of the pre-clinical NHP work into clinical research as this could lead to new collaborative programs with other teams of the center or the Vaccine Research Institute.

The methodological approaches are breakthroughs but the theoretical approaches need to be reinforced.

The proposed project, the impact of which is excellent, is a leading investigation of mechanisms of immune responses to infectious diseases in NHP that is expected to generate very important and high quality results with both biological and clinical implications.

This group is devoted to infection and studies host-pathogen interactions, focusing on several pathogens in NHP primates. It has four main objectives: the study of mechanisms of induction of the anti-viral responses, the study of innate responses at the site of initial events and in the draining lymph-nodes, the characterization of biomarkers, and finally the study of correlates of protection. The challenging NHP models developed are one of the most important aspects of the project. The team benefits of an exceptional environment and funding to perform the programme. It has been very successful in obtaining peer-reviewed grant support and in recruiting young scientists.

The part of the project dedicated to study various parameters of vaccination and mechanism of immune responses is low-risk. The team should be more ambitious and take some risks.

The overall assessment strategy for career evolution and leadership delegation to young and senior scientists could be better defined in the five-year plan.

Conclusion

- **Strengths and opportunities:**

- focus and shrewd strategic leadership of the lab;

- state-of-the-art expertise on the manipulation of NHP;

- IDMIT platform.

- **Weaknesses and threats:**

- the program will require go-no-go decision on the relevance of the different technological approaches depending on their predictive values and the capacity of the team to interpret complex data sets;

- the capacity to translate NHP results in human clinical research.

- **Recommendations:**

- bio-computational aspects should be reinforced.

5 • Conduct of the visit

Visit date:

Start: Wednesday December 4th 2013 at 8.00 am

End: Wednesday December 4th 2013 at 6.00 pm

Visit site:

Institution: CEA

Address: 18 route du Panorama, Fontenay-aux-Roses

Conduct or programme of visit:

08.00 am	Closed-door meeting: expert committee members and AERES Scientific Delegate (DS)
08.30 am	Presentation by the head of the unit: past activity and projects
09.00 am	Team 1 - Control of Chronic Viral Infections (Mr Olivier LAMBOTTE)
09.45 am	Team 2 - Normal and Pathological T cell-memory (Mr Yassine TAOUFIK)
10.30 am	Coffee break
10.45 am	Team 3 - New mechanisms involved in pathogenesis of autoimmune diseases (Mr Xavier MARIETTE)
11.30 am	Team 4 - Viral transmission, antiviral Immunity, and vaccines (Mr Roger LE GRAND)
12.15 pm	Lunch-buffet
01.45 pm	Meeting of the experts committee with representatives of the Université Paris-Sud, the CEA, and Inserm
02.15 pm	Meeting of the experts committee with a representative of the PhD-program (ED425) of the Université Paris-Sud, Prof. Karl BALABANIAN
02.30 pm	Three parallel meetings of the experts committee with: - PhD students and postdoctoral fellows - engineers, technicians and administrative assistants - researchers with permanent position (except the unit's director and team-chiefs)
03.15 pm	Closed-door meeting of the experts committee and DS with the unit's director
03.45 pm	Tea-break
04.00-06.00 pm	Closed-door meeting of the experets committee and DS

6 • Supervising bodie's general comments

UNIVERSITÉ PARIS SUD

Comprendre le monde, construire l'avenir®

Le Président de l'Université Paris-Sud

à

Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
AERES
20, rue Vivienne
75002 Paris

Orsay, le 19 mars 2014

N/Réf. : 53/14/JB/LM/AL

Objet : Rapport d'évaluation d'unité de recherche
N° S2PUR150007963

Monsieur le Directeur,

Vous m'avez transmis le 24 février dernier, le rapport d'évaluation de l'unité de recherche - - Immunologie des maladies virales et autoimmunes - N° S2PUR150007963, et je vous en remercie.

L'université se réjouit de l'appréciation portée par le Comité sur cette unité et prend bonne note de ses suggestions.
Elle suivra avec une attention particulière la mise en place de ce centre de recherche et de son ambitieux projet scientifique, de premier plan international.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de ma sincère considération.

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Jacques BITTOUN
Président

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Agence d'Evaluation de la Recherche
Et de l'Enseignement Supérieur
20 rue Vivienne 75002 PARIS

Comité d'Evaluation de l'unité de recherche mixte « Immunology of Viral and Autoimmune Diseases »

Chers Collègues,

Je vous remercie pour le rapport d'évaluation de notre unité de recherche et du projet de création de la structure de recherche mixte associant l'Université Paris Sud-11, le CEA et l'INSERM et intitulée « Immunology of Viral and Autoimmune Diseases ».
L'ensemble des chercheurs responsables des futures équipes, ainsi que moi-même, en tant que porteur du projet, nous souhaitons souligner la grande qualité du rapport qui nous a été transmis ainsi que des discussions engagées lors de la visite du comité. Il en ressort des commentaires, à la fois sur les orientations scientifiques et l'organisation de la structure, qui nous sont apparus particulièrement pertinents et constructifs et que nous prendrons en compte pour la mise en place de projet.

Cordialement,

Roger LE GRAND
UMR E1, Univesité Paris Sud-11
Service d'Immuno-Virologie, CEA

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