A2T - Alloimmunité - autoimmunité - transplantation

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Alloimmunity-Autoimmunity-Transplantation

A2T

Under the supervision of the following institutions and research bodies:

Université Paris 7– Denis Diderot

Institut National de la Santé Et de la Recherche Médicale

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

Research Units Department

President of AERES

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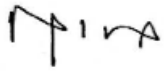


Pierre Glaudes

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: Alloimmunité-Autoimmunité-Transplantation - A2T

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

- Grading table of the team: Lymphocyte differentiation and homeostasis in allo- and autoimmunity

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

- Grading table of the team: Allogeneic responses in renal transplantation

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

- Grading table of the team: Hematopoietic stem cell transplantation

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

Evaluation report

Unit name:	Alloimmunity-Autommunity-Transplanation
Unit acronym:	
Label requested:	UMR_S
Present no.:	
Name of Director (2012-2013):	
Name of Project Leader (2014-2018):	Mr Antoine TOUBERT

Expert committee members

Chair: Mr Ignacio ANEGON , University of Nantes

Experts:

Ms Susan CHAN, University of Strasbourg (INSERM representative)

Mr Paolo DELLABONA , San Raffaele Scientific Institute, Italy

Mr Matthias EDINGER, University of Regensburg, Germany

Mr Gunther EISSNER, University of Munich, Germany

Mr Yvon LEBRANCHU, University of Tours (CNU representative)

Mr Alain LE MOINE , University of Charleroi, Belgium

Mr Riccardo SACCARDI , University of Firenze, Italy

Scientific delegate representing the AERES:

Ms Sophie DE BENTZMANN

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

Ms Christine CLERICI, Paris 7 University

Ms Laurence LOMME, INSERM

1 • Introduction

History and geographical location of the unit

This is a new unit asking for INSERM recognition. Team 1 and 2 were part of a previous INSERM unit (U 940) and members from team 3 were formely members of another INSERM unit (U 728). Team 1 and 2 have new researchers from the St. Louis and Lariboisiere hospitals (as for example from Intensive care department or from INSERM units outside this campus). All of these teams were and will be located in the Saint-Louis Hospital campus and will be part of the Institut Universitaire d'Hématologie (IUH).

Management team

The unit will be headed by Mr Antoine TOUBERT.

AERES nomenclature

SVE1_LS6

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	6 (1,8)	14 (4,2)	6 (1,8)
N2: Permanent researchers from Institutions and similar positions	5 (5)	5 (5)	4 (4)
N3: Other permanent staff (without research duties)	13 (6,7)	16 (9)	
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)			
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	4 (2,6)	5 (3,6)	4 (2,6)
N6: Other contractual staff (without research duties)	2 (2)	2 (2)	
TOTAL N1 to N6	29 (18,1)	42 (23,8)	14 (8,4)

Percentage of producers	***93.3%***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	8	
Theses defended	5	
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	7	14

2 • Assessment of the unit

Strengths and opportunities

The presence in the same INSERM unit of kidney and hematopoietic cell transplantation is important and useful.

The presence of allotransplantation and autoimmunity is also interesting and important.

The proposed unit has strong clinical environment and clinicians directing important clinical departments (gastroenterology, renal transplantation, bone marrow transplantation, cell therapy, intensive care) or clinical laboratories (immunology, immunogenetics) are part of the unit.

Most of the PIs of the new INSERM unit have previously worked together with a good track record of common papers and funding.

There is a very good scientific and technical (platforms) environment in the Institut Universitaire d'Hématologie, which is part of an IDEX and is a promising IHU, as well as a partner of Labex projects.

There are a very good insertion and connections with master and medical students.

Several of the unit PIs have a very good to excellent international visibility and reputation .

Mr Antoine TOUBERT has an unanimous recognition according to the committee as a leading figure and with the recognition and authority to be the Director of the new unit.

Several clinical projects are ongoing among which are PHRC (LYMPHCORD and APCORD) and FP7 "STEMEXPAND".

Weaknesses and threats

Some of the components of the project are not clearly integrated in the research project, although clinically very well integrated for a long time. This is the case of the CICT "cell therapy facility", extremely important in the clinical practice of bone marrow transplantation but not obvious in the research project . The CICT has expertise in the therapeutic use of mesenchymal stem cells (MSCs) but there is no therapeutical application of MSCs in the area of the unit proposal; as an example, there are apparently clinical trials to be performed in other autoimmune diseases but not in Crohn's or Human Stem Cell Transplantation (SCT). Analogously, the committee felt that the expertise of the CICT in the use of cord blood cells to perform bone marrow transplantation could be the basis for projects on cell biology or on the manipulation or on their cell culture and in vitro expansion to be used in transplantation.

Another component with no clear specific research project and added value is the immunogenetics, since these approaches are extremely important for HLA typing for clinical kidney and bone marrow transplantation as well as for more research oriented projects, such as non-classical HLA I antigens. However, there is no clear research project of this group. It seems rather like a common platform or transversal resource rather than as a research group.

The committee underlined the weak presence of full time basic scientists, particularly in team 3 (none), also in team 1 (only 1 now and a second one in 2014). There are 3 in team 2.

Recruitment of post-doctorants should be increased, particularly in team 3 (none) and 2 (one).

There are few technical positions in team 3 and 2 despite that in 2014 the organization chart shows 3 for this last group which should be a reasonable number considering the number of researchers.

One aspect which has to be mentioned is the presently limited access to structured bioinformatics/biostatistics.

The committee has the feeling that there are not enough industrial or clinical valorisation projects. For industrial valorisation/collaborative projects, there was one project on the use anti-NKG2D antibodies in Crohn's disease but there is no clear indication of others in the pipe line. As far as clinical valorisation projects, the committee thinks that it may be still soon for the use of some of the scientific findings to be used in the clinics, as an example biomarkers, and this should be an important objective for the future.

Recommendations

The unit has to increase attractivity for basic researchers and post-doctorants. There is a movement in this direction since 2 permanent researchers will join team 1 but there is none in team 3. One strategic point is to implement the access to bioinformatic/biostatistic analysis.

Industrial, and mainly clinical valorisation should be emphasized, since the strong clinical environment gives to this INSERM unit a strategic and unique advance for this type of applications.

3 • Detailed assessments

Assessment of scientific quality and outputs

Not applicable since the unit is a new one.

Assessment of the unit's academic reputation and appeal

Not applicable since the unit is a new one.

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

Not applicable since the unit is a new one.

Assessment of the unit's organisation and life

Not applicable since the unit is a new one.

Assessment of the unit's involvement in training through research

Not applicable since the unit is a new one.

Assessment of the five-year plan and strategy

The scientific topics of each team of the unit are in general very good although in each of the 3 teams there is a need for more focus. The presence in the same INSERM unit of a team working in immune reconstitution and role of NK and T cell subsets in bone marrow transplantation (team 1) and another one in kidney transplantation (team 2) as well another team in graft versus host disease (GVHD) (team 3) is important, original and potentially very useful. Nevertheless, for the cross-talk among these different components to be productive, the number of transversal and common projects between the teams should be reinforced.

The topic of autoimmunity and inflammation, or more precisely of Crohn's disease from the "Avenir" group, is at the first sight less integrated with the other main topic of team 1, immune reconstitution after bone marrow transplantation, but in fact the accent of the autoimmunity group on the analysis of cells or molecules of the innate immune responses (iNKT, NK, NK2GD) as well as T cell substes integrates well with the expertise of the rest of Team 1.

The group working on brain death donors is new in the unit (part of team 2) and strategically important to address issues such as endothelial cell status in these donors which may very likely have an impact on kidney graft function and/or survival. Their projects are well interconnected with those of the rest of team 2. Nevertheless, some seem too ambitious and with low feasibility.

The availability of lab space as well as of permanent researchers for team 3 is clearly identified as a very important objective and is definitively seen by the evaluation committee as a strategic priority. It would also be important to have this lab space in proximity with the other teams.

Biobanking should also be a priority and has been recently funded by a specific program (CRYOSTEM).

Development of animal models and in vitro mechanistic studies has also been identified as a priority for the future years and the committee supports this initiative.

The unit has to increase and better structure internal and external communication :

As the unit is in creation there are no meetings yet of the teams together but one is planned per month for a scientific meeting, which is good.

No mention of meetings between the PIs from the different teams to discuss logistics, funding, scientific and technical priorities, grant proposals was made but this has to be settled, a point that has to be applied also to regular lab meetings for each team and not only to weekly journal clubs for students that already exist.

The lack of obvious external communication process with the rest of the Institut Universitaire d'Hématologie has to be reinforced in the form of meetings, definition of common strategies, integration with other INSERM units.

External seminars in the frame of "Jean DAUSSET seminars on Immunology and Histocompatibility" have been organized since 2010 by the unit in the IUH.

4 • Team-by-team analysis

Team 1 : Lymphocyte differentiation and homeostasis in allo- and autoimmunity

Name of team leader: Mr Antoine TOUBERT

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 (1,2)	5 (1,5)	4 (1,2)
N2: Permanent EPST or EPIC researchers and similar positions	2 (2)	2 (2)	1 (1)
N3: Other permanent staff (without research duties)	9 (4,6)	9 (5,3)	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3 (2,3)	4 (3,3)	3 (2,3)
N6: Other contractual staff (without research duties)	2 (2)	2 (2)	
TOTAL N1 to N6	20 (12,1)	22 (14,1)	8 (4,5)

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	5	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	3	6

• Detailed assessments

Assessment of scientific quality and outputs

Both scientific quality and output of the team in its composition until 2012 have been excellent. The team is focused on understanding the host immune status (T and NK cell differentiation and function) following allogeneic hematopoietic stem cell transplantation (allo-HSCT), with smaller projects on the characterization of MHC class I-related chain A molecules during graft versus host disease, NK cell function in acute myeloid leukemia (AML), and the immunopathology of inflammatory bowel disease (IBD). More recently, the group has integrated a project to study two new populations of "innate lymphocytes" that might play a role during HSCT and IBD, namely: IL-17-secreting RORgt+ iNKT cells and MAIT cells. All of these projects are in the human system, and take good advantage of the hospital environment and the medical expertise of the group leaders. They make use also of well designed animal models to gain mechanistic insights.

The team has published 18 papers in good (IF 5-10) to very good (IF 10-15) journals as first or senior authors (Blood, Gastroenterology, Plos Pathogens, Sci Transl Med, J immunol, J Infect Dis). The group has also published more than 20 papers in collaborative studies. Further, the Avenir group leader has published 39 clinical papers with many multicenter trials of therapeutic strategies of IBD (N Engl J, Lancet) and 2 Gastroenterology on NKG2D CD4 Tcells producing IL-17 in CD.

The team is undergoing major changes with the arrival in 2012 of a CR1 INSERM researcher and the arrival of a DR2 INSERM researcher in 2014 with a a very good record of publications (33 articles ISI Web of knowledge, h-index of 20 and 102 articles ISI Web of knowledge, h-index of 25, respectively).

Assessment of the unit's academic reputation and appeal

The team is very well recognized both nationally and internationally. It has been successful in securing funding (total amount unknown for 2007-2012) through competitive grant applications at the national level (INCa, Contrat de Recherche Translationnelle, Cancéropole Ile-de-France, Association Laurette Fugain) as coordinator or as partner. The team was a partner of a EC FP6 integrated project grant and also received a grant from AMGEN. The recipient of the Avenir starting grant is a partner of a European Innovative Medical Initiative. The team is involved as partners of 2 Labex projects, as well as a Contrat d'Interface AP-HP/Inserm.

The team leader has been invited to speak at international and national meetings. He was member of the Immunology scientific commission (CSS5) at Inserm from 2008-2012, is secretary of the EBMT (European Bone Marrow Transplantation) Immunology Working Party, is program manager of the ANR committee SVSE3, is Chief Editor of Frontiers in Alloimmunity and Transplantation, he is part of the EU network project ERA-NET TRANSCAN Haplo-immune 20013-15.

The Avenir leader has given many seminars worldwide. He is chief officer of the European Crohn's and Colitis Organization (ECCO) and has helped organizing a number of meetings in Europe and in the US. He is in the scientific commissions of 2 French charity organizations (AFA, AFDIAG). He is also involved in several translational (ABIRISK) and therapeutic international trials of IBD patients

Other team members have also participated actively in international meetings. The CR1 recruited in the team in 2012 is well known in the NKT cell field for his fundamental studies on developmental mechanisms. The DR2 INSERM joining in 2014 is a well-respected scientist in NK cells and tumors.

Additional highly qualifying aspects of Team 1 that support their attractiveness and visibility are the contrat d'interface on NK cell development topic, the Poste d'accueil INSERM, the partnership in 2 Labex consortium, the recruitment by the Avenir leader of a highly qualiied post-doctorant expert of MAIT cells (Nat Immunol 2010).

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

The team is well immersed in the local, national and international social, economical and cultural environment. Connections are made through the participation in multicenter fundamental translational and clinical projects, which involve both academic and industrial partners. Locally, there are very good interactions with hematology and gastroenterology clinical departments. The team has published a guideline for preventing infectious complications in HSCT patients (Bone Marrow Transplant). The Avenir leader has given several conferences for patient associations. There are connections with companies (Novo Nordisk and Amgen and Innate), although this and clinical valorisation should be improved for a team mostly involved in translational clinical/biological research.

Assessment of the unit's organisation and life

The organisation of the team is fairly straightforward, in compliance with the international standards for research organization. Emphasis seems to minimize a rigid hierchical structure in favor of more dynamic relationships, which should foster scientific interactions and creativity.

As communication is concerned, there are weekly journal clubs. Meetings are also organized with clinical teams on a project basis, but this does not seem very structured, as for common seminars of the teams and lab meetings per team. Few seminars were organized by the IHU.

Assessment of the unit's involvement in training through research

The team has supervised 4 postdoctorants, 9 PhD students and 12 Master students. Several team members teach modules in different Master courses at the Universities Paris 5, 6, and 7, and at Institut Pasteur. Several members of Team 1 are involved in teaching activities in Masters and the team leader is coordinator of modules in 2 masters.

Assessment of the five-year plan and strategy

The five-year project plan proposed by this team is sound. It represents the logical continuation of the research objectives undertaken by each single component of the team, reformulated in the light of the opportunities offered by the merging of the newly recruited scientists in the team. This should allow the exploration of new original questions in the field of alloresponses, bone marrow transplantation and autoimmunity/chronic inflammation. The plan is based on a balanced blend of projects addressing fundamental aspects of immunobiology as well as unmet medical needs related mainly to bone marrow transplantation, leukemia and IBD. In detail, the main goal of the team is to evaluate how different pathological contexts can impact lymphocyte differentiation and function which in turn affect the disease process. The group proposes to continue and expand their current work. Four projects are proposed: 1) Lymphocyte differentiation and maturation following allo-HSCT, 2) NK cell function in AML and myelodysplastic syndromes, 3) iNKT cell development and function; 4) Immunopathology of IBD. The work of the DR2 INSERM will be integrated in Aim 2. These projects are independent, but complementary and well integrated and benefit from each other in terms of expertise and reagents.

The projects appear to be appropriate and address important questions. However, as the team acknowledges, the tasks are vast and it will be important to remain focused. Project 2 deals with immunogenetics in allos-HSCT and myeloid malignancies and aims to analyze NK cell receptors and ligand polymorphisms in AML and CML, but there are no preliminary results or published results from other groups to give support to this work. The team did publish in 2006 a J. Immunol. paper on MICA antigen expression in CML but the link to this project on polymorphism is not that clear. This is the only project of the immunogenetics group within team 1, which is a rather numerous group. The project is led by a PH medical doctor and this raises the question whether there will be effective time of research for this project.

Project 3 is extremely competitive and it will be important to find a niche for this topic.

The development of immune humanized mouse models is important and ambitious and the contrat d'interface with a PI from Pasteur Institute seems very appropriate.

Project 4 (Immunopathology of IBD) by the Avenir leader is very interesting, ambitious and feasible because the Gastoenterology Department follows one the largest cohort of IBD (> 5000), it has tight links with industry (Novo Nordisk for exemple in a trial of NKG2D receptor blockade) and competitive fundings from European communauty (BeTheCure). There also very good interactions and integration with the others members of the team. The project proposes to analyze IBD ligands (like MICA) of NK2D+ T cells on intestinal epithelial cells and this is logical but could also consider to analyze the expression of these same ligands on intestinal endothelial cells which could be a collaboration with team 2.

The AVENIR group future is not envisioned as a new group in a short time period by its leader due his clinical duties. The recruitment of a highly qualified post-doc expert of MAIT cells (Nat Immunol 2010) in this AVENIR group, is very good and may give more consistency to the emergence of a new team, an option sustained by the Director and that has to be prepared.

Conclusion

- Strengths and opportunities:

The team is internationally recognized for their work and expertise and had a very good scientific production.

The team gathers PIs with international caliber and visibility.

The project displays a good assortment of directions and well defined and original scientific questions. The project will benefit from an excellent integration with the clinics.

There is a solid background on the different topics that are the main objectives of the project (thymus and HSCT, NK cells, myeloid malignancies) expanding to other cell types like iNKT and innate lymphoid cells (ILC).

The team has demonstrated ability to attract a talented workforce.

The team can benefit from updated technological platforms available.

The team members have the capacity for the development of new modelling to address the specific questions.

There is a ready possibility to translate into pilot clinical studies the results of basic and preclinical research.

- Weaknesses and threats:

The team is still going through a major transition with the recent and upcoming integration of new subgroups. As a result, the 5-year strategy is diverse. It is important that the goals remain focused, and that the Avenir group becomes independent in a mid-term perspective.

There is a potential danger to become "top heavy" in that there are many project heads and less trainees.

There is a limited access to in house bioinformatics and statistics.

The team hosted few foreign students (some from an ECOS Nord program) and no foreign post-doctorants or researchers.

Communication and discussion within the team are not clearly defined.

- Recommendations:

The team should focus on major research axis.

There is a need to structure comunication amongst team members to foster collaborations and exchange of ideas.

The team has to keep “bed-to-bench” research axis always very active, in order to exploit observations from the clinics to investigate new aspects of fundamental immunobiology to solve unmet medical need.

The team has to strength access/collaboration for bioinformatics and statistics.

Effort has to be made on integration into european networks on education and training to increase international recruitment.

Team 2 : Allogeneic responses in renal transplantation

Name of team leader: Ms Nuala MOONEY

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 (0,6)	5 (1,5)	2 (0,6)
N2: Permanent EPST or EPIC researchers and similar positions	3 (3)	3 (3)	3 (3)
N3: Other permanent staff (without research duties)	4 (2,1)	4 (2,1)	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1 (0,3)	1 (0,3)	1 (0,3)
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	10 (6)	13 (6,9)	6 (3,9)

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	4	5

• Detailed assessments

Assessment of scientific quality and outputs

Publication track record is good to very good in the field (impact factors do not necessarily reflect the scientific quality), very good interdisciplinary research. From 2007 to 2012 publications in J. Leuk. Biol. (1), Eur. J. Immunol. (2), Am. J. Transplantation (5), J. Am. Soc. Nephrol. (1), PNAS (1), J. Immunol. (2), Clin Exp Immunol (1),Transplantation (1) and Plos One (1).

Assessment of the unit's academic reputation and appeal

PIs are invited in international meetings. One has been an organizer of a Banff workshop, is the President of the French Society for transplantation (SFT) and received a prize from the Am. Soc. Histocompatibility. The team leader is known and respected in the community of immunologists for her contributions about the role of class II antibodies and of the endothelium in graft dysfunction. The team leader is member of European evaluation committees. The team has hosted a "posted'accueil 2009-2012" and is involved in the LABEX " Transplantex", the DIM " Biothérapies" and the FPZ-HEALTH-2012-INNOVATION-1 program.

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

There is at least one article in a general journal. One of the PIs has a "public notoriety" at least as President of SFT. Outreach activities could be intensified, especially because the program is of great health economic relevance and the sophisticated scientific and methodological approaches need elaborate explanations for the public. There are some patents, but on the area of intensive care and not in immunology or transplantation. Funding is limited except from Roche Organ Transplantation Research Foundation (ROTRF) to the team leader and part of Labex Transplantex. There are no apparent funding or collaborations with industry.

Assessment of the unit's organisation and life

The PIs have a good track of common publications but the team is being reshaped and communication will be very important. The schedule of regular lab meetings does not appear clearly even if regular journal clubs are performed.

Assessment of the unit's involvement in training through research

The team has a very good track of PhD and master students having done their laboratory work. 4 PhD students finished their thesis and 3 are underway. There are 2 students from Colombia through ECOS-Nord. The team leader is very active in international education via Marie Curie Training Networks of the European Commission. Members of the unit are involved in teaching programs from Masters Paris 7, Paris 11, ENS Cachan and ESOT course.

Assessment of the five-year plan and strategy

Overall, the projects are of high quality, highly fundable and use straightforward approaches and state-of-the-art technology, addressing previously unmet immunological questions about renal allograft survival and contain translational aspects (patient serum, clinically usable signal transduction inhibitors). Nevertheless, there are some concerns about the feasibility (particularly of project 3) and a too big number of different projects taking into account the relatively small size of the team.

Project 1 (ECs and anti-MHC II in kidney chronic rejection) is a logical continuation of previous work of part of the team with clinicians. Task 1, part 1.1, although the cellular tools for analyzing endothelial-specific immune activation processes are well chosen, the originality and importance are questionable. There are some points that may be more interesting than others, such as comparison of different cell types and haplotype-specificities. Concerning the signalling pathways induced by anti-class II antibodies the committee raised questions about specificity, dose dependency, role of preactivation of EC, accommodation or not, comparison with xeno antibodies.

Part 1.2 seems more original since it will address the localization of MHC II antigens in lipid rafts or tetraspanin microdomains and how anti-MHC II antibodies modify the interaction with CD4+ T cells and potential specificities of the endothelium as compared to professional APC (B cells, DC) to present antigens to T cells.

Nevertheless, the techniques available (like confocal and time lapse or other imaging techniques to analyze the immune synapse) and expertise on these techniques are not very clear. Similarly, all the studies seem to be limited to in vitro interactions and the possibility of analyzing tissue biopsies using confocal microscopy in order to analyze the immune synapse are not mentioned. This type of analysis has already been used, as an example in the CNS between CD8+ T cells and target astrocytes. Some additional aspects could have been involved (e.g. induction of cytotoxic / class I-restricted responses, role of immune suppression (rapamycin, CsA, etc.) for endothelial function/viability, nature of DSA-induced alloresponses (endothelial-specific or not). There is a similar feeling with functional assays assessing the role of ICAM-1.

Tasks 2, 3 and 4 (this last one using immune humanized mice grafted with human vessels) are more focused, novel and ambitious. Task 3 is clinically relevant and critically challenging current drugs. A clinical relationship with a possible involvement of Th17 in some humoral rejections could be interesting. For task 3 others biomarkers of EC activation, such as soluble adhesion molecules, could be studied. Task 4: Well designed in vivo approach, ambitious and very interesting, having the benefit of the very good expertise of a team in these humanized murine models.

Project 2 (mechanisms of anti HLA class II antibody pathogenesis) contain a task 1.1 aiming to define the phenotypic evolution of B cell lymphocyte subsets in ATG and IVIG-treated patients. B cells of ATG-treated patients are depleted but plasma cells likely not and the reconstitution of B cells is not well established but these objectives are not mentioned, nor whether this will be done in patients treated with low doses of ATG. Already published papers from other groups on this topic analyzed low and ultra-low doses and showed that B and plasma cells were not depleted. Task 1.2, PBMC will be stimulated with B cell stimuli and anti-MHC II antibody production will be analyzed by Luminex. This is interesting but it is not specified in which patients. The rationale for the experiments in Task 1.2 could have been better described (stimulation with BAFF, etc). Additionally, B cell subset changes and alloantibody production over 24 months after ATG could depend on the immunosuppressive regimen. Task 1.3.2 proposes to analyze the antigen presenting capacity and the alloantibody production of CD86+ or CD86- B cell subsets (with higher and lower MHC II expression, respectively); this task seems interesting and novel. Task 2.1 proposes to detect antibodies activating C1q rather than C4d but the limitations of C4d detection are not obvious and therefore the possible advantage of C1q neither; there is no mention of detecting both C1q and C4d in order to compare both methods. For Tasks 2.2 and 2.3 details are lacking how precisely the histological findings will be correlated with the anti-C1q-antibody titer assessment and some concerns about originality. This project has the benefit of the very good clinical expertise of PIs of the team on antibody-mediated rejections (Lancet 2013). Nevertheless, tasks 2-1 and 2-2 are very competitive and not very original. More details are needed for task 2-3. This should include sensitized patients and even be focused on them.

Project 3, task 1, is innovative and exciting and could be an important contribution to the understanding of endothelial function of the graft following brain death. There are concerns on how to reproduce in endothelial cells from brain death donors cultured in vitro the inflammatory and metabolic situation found in vivo. In this regard, the project, although not very clear in its written version, is based on the culture of these endothelial cells adding serum from the brain death donor patients but the group does not have preliminary results in this model. Task 2, although the identification and functional analysis of monocyte subsets is ambitious and innovative there are concerns about the feasibility of this highly competitive project. Task 3 and 4, are interesting and feasible. Task 5 (in vivo studies for the role of monocytes and DCs in a mouse model of heart allotransplantation) seems not very original and there is no specific knowledge on this transplantation model or in mouse immunology in the team. The methodology could have been described in more detail to show the originality and innovative nature of this task, e.g. which particular anti-donor anti-serum (taken after transplantation) will be used instead of donor PBMC to investigate the key factors leading to monocyte graft infiltration. Remaining focused on human samples (tissue EC etc…) should be a priority. The use of the mouse immune system humanized model could have been more appropriate to maintain the human immunology profile of their research and to collaborate with team 1 of the unit to generate a single animal model and not two. On the other hand, the mouse immune system humanized model is more difficult to set up versus the allogeneic mouse model.

Conclusion

● Strengths and opportunities:

Excellent clinical and translational research with very good expertise in kidney vascular rejection and in the ability of EC to orient the alloimmune response.

Publication track record is very good.

High potential with strong interactions with the Nephrology Department as evidenced by high quality published papers analyzing anti-HLA antibodies.

Interdisciplinary scientific and methodological approach meeting previously unmet pathophysiological questions, e.g. in how far the donor contributes to graft rejection. There are also interactions with the Intensive Care Department, 2 papers published between 2007-2012 with the INSERM team but clearly integrated in the project.

● Weaknesses and threats:

It appears that there is a technical staff shortage, especially with regard to the comprehensive and ambitious program (extensive cell culture, histology, etc.). The documents indicates 0.5 technical position from 2007-2012. The organization chart for 2014 at the end of the book “Projet scientifique” indicates 2 engineers and 1 technician. If this is the case, it is clearly an improvement versus the last period but still the number of projects is too important.

There have been 7 common papers between PIs. This is a good track but should be increased and common projects strengthened. In the project, there is weak collaborative networking recognizable (neither scientific nor technological) with the other teams of the unit which usually is the purpose of such a consortium. The areas of DC or monocyte biology are very competitive and the impact of the publications does not seem very strong; collaborations could help to include more novel techniques and concepts.

● Recommendations:

The need to increase the number of technical positions is underlined although the organization chart for 2014 at the end of the book “Projet scientifique” indicates 2 engineers and 1 technician. Effort has to be made to reinforce collaborations and interactions within the team and with other teams. The task 5 of project 3 is not recommended to be undertaken (remaining focused on human). The team has toregularily perform lab-meetings with the different PIs of the team as well as with other units’ teams.

Team 3 : Hematopoietic stem cell transplantation

Name of team leader: Mr Gérard SOCIÉ

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	NA	4 (1,2)	NA
N2: Permanent EPST or EPIC researchers and similar positions	NA		NA
N3: Other permanent staff (without research duties)	NA	3 (1,6)	NA
N4: Other professors (PREM, ECC, etc.)	NA		NA
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	NA		NA
N6: Other contractual staff (without research duties)	NA		NA
TOTAL N1 to N6	NA	7 (2,8)	NA

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

• Detailed assessments

Assessment of scientific quality and outputs

The team leader has a very good publication record for the years 2007-2012 (as first or last author: 5 in Blood, impact factor of 9.8). He is head of the stem cell transplantation unit at Hospital Saint-Louis, the largest transplantation center in France. The group is highly recognized in the field for their clinical expertise in hematopoietic stem cell transplantation and GVHD. Furthermore, they pioneered cord blood transplantation in Europe. Scientifically, the team leader studied clinical GVHD with a focus on endothelial and gastrointestianal damage. Using mainly patient samples, the group described relevant biomarkers of GVHD. The team leader is member of the Editorial Board of "Blood" and "Biology of Blood and Marrow Transplantation (BBMT)", President of the French Society of Hematology, and received prestigeous research funds from national and European agencies (e.g. FP6 and FP7 funds from the EC). He is well connected within the research community and highly recognized for his clinical and scientific expertise.

One of the PIs, heading the Department of Cellular Biothérapies and of the cord blood bank in Hospital Saint-Louis has a very good publication record for the period 2007-2012 (as first or last author: 2 in British J. Haematol., impact factor of 4.9; 3 in Stem cells Dev., impact factor of 4.5; and 1 in Leukemia, impact factor of 9.5). He is thus centrally involved in the stem cell transplantation (SCT) program and a key figure for the cord blood transplantation (CBT) program that was pioneered by the Paris group in IUH. As a PI he extensively collaborated with various other groups, but also published independent research findings as first and senior author.

One of the PIs, heading the immunogenetics laboratory in Hospital Saint-Louis has a good publication record for the years 2007-2012 (as first or last author: 1 Blood; 1 Transplantation, impact factor of 3.5; and 1 Bone Marrow Transplantation). She is internationally involved in HLA-typing and quality control, the discovery of gene polymorphisms and the genetics of non-HLA genes. As general secretary of the French Histocompatibility and Immunogenetics Society she is internationally visible for her scientific expertise.

Assessment of the unit's academic reputation and appeal

The team leader is one of the world experts in GVHD including both, its clinical presentation and therapy as well as GVHD biology and immunology. He is regularly invited to national and international meetings, co-editor on a comprehensive book on GVHD, editor for main journals in the field and he collaborates internationally with the main clinicians and research groups in the field. As member of scientific committees, he is involved in the organisation of international clinical and scientific meetings in SCT (American Society for Hematology, European Hematology Association, European Group for Blood and Marrow Transplantation, Blood and Marrow Transplantation , French Society of Hematology). He is president of the French Society of Hematology and member of the ITMO INSERM.

The PI heading the Department of Cellular Biothérapies and of the cord blood bank in Hospital Saint-Louis plays a pivotal role for the processing and manipulation of hematopoietic stem cell products including cord blood and thus is crucially involved in the SCT program at Hopital Saint-Louis. Beside this, he has good national and international collaborations and participates to the national commission for the evaluation of medical products (Afssaps). He is partner in EC-funded international collaborations (FP6, FP7) thereby progressing SCT research on an international level. His expertise in clinical cell manipulation permitted the development of a cord blood bank and the development of a CBT program, the leading and most prestigeous program in Europe. Together with others he is involved in the CRYOSTEM consortium that develops biobanking strategies nationally and also at Hospital Saint-Louis.

The PI heading the immunogenetics laboratory in Hospital Saint-Louis has a good reputation in the field of HSCT Histocompatibility. Overall the Unit has an excellent reputation in the relevant fields.

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

Taken together as a clinical group managing the largest SCT center in France, team 3 has a major impact on the life of transplant patients and a large influence on SCT strategies and research in France. The team leader regularly teaches at the European School of Hematology and therby influences the education of young transplanters throughout Europe. Their contribution to the respective research societies contributes to the advancement of the field on a national and international level.

Members of the group received some fundings from private companies but do not seem to have exploited potential clinical and economical valorization of their research .

Assessment of the unit's organisation and life

All three researchers of team 3 closely collaborated in the past for the clinical management of the SCT program. The researchers published together with team 1 on the topic of immune reconstitution after SCT. Yet, collaborations could be further formalized and intensified between the PIs of this team and with other teams of the proposed INSERM unit by organizing regular joint seminars. During the site visit it was evident that team 3 is not yet fully integrated into the consortium and the PIs should thus be encouraged to further intensify their efforts.

Despite the very good publication record of the team leader,it is obvious that his research thus far depends strongly on external collaborations (e.g. Dept. of Pathology, Institute Pasteur, EU partners, US partners). Although the SCT program is the largest in France, there is no institutional support for research as this PI has no dedicated research laboratory nor professional research staff (neither scientists nor technicians). For the successful implementation of this INSERM unit, it is indispensable to provide the members of team 3 with an appropriate infrastructure (e.g. laboratory space and personnel such as a senior scientist, a PhD student position and 1-2 techicians).

Assessment of the unit's involvement in training through research

The PI heading the Department of Cellular Biotherapies and of the cord blood bank in Hospital Saint-Louis is responsible for the teaching of Cellular Biology and coordinates teaching of 2 sections of master courses. The PI heading the immunogenetics laboratory in Hospital Saint-Louis is involved in national and international societies in the field of histocompatibility and the team leader teaches within the European School of Hematology and is director of doctoral thesis programs for medical students and PhD students. With the improvement of their research environment, the number of master and PhD students trained by team 3 could and should be increased.

Assessment of the five-year plan and strategy

The team has mainly two projects.

One research project will focus on the immunobiology of GVHD and thus extends their previous strategy in the evaluation of biomarkers using clinical samples. The plan is now to evaluate the role of different B cell subsets in GVHD pathophysiology and to perform gene expression arrays from whole blood as well as defined lymphocyte subpopulations in patients with and without GVHD after allogeneic SCT. Preliminary own and external data have been presented and represent an outline of the research plan that is scientifically sound, in line with his previous work and potentially clinically relevant. Due to the high number of patients transplanted at the institution and the proven ability to retrieve, bank and analyze clinical samples, the project seems feasible and the PI exceptionally qualified to perform the research task. By nature, such studies primarily generate correlative data and an accompanying animal model would be suited to better examine mechanistic processes and overall strengthen the research project. Yet, such models could only be established if the basic research infrastructure for the group is improved. The gene expression analyses will be performed in collaboration PI of the team and external partners (Pasteur Institute) that are experts in these fields and technologies. Nevertheless, it is a risky project and even large cooperative groups frequently failed to discover relevant signatures of tolerance. Despite this caveat, the committee thinks that it is worth exploring this topic but only if sufficient biostatistical support is provided.

The other project will focus on the one hand on asymmetric cell division with an emphasis on mesenchymal stroma cells (MSC). On the other hand on the role of MSC in health and disease (myeloma, systemic sclerosis, BM failure, BM microenvironment) and on their immune modulatory properties. It is planned to examine the influence of toll-like receptor ligation on MSC and hematopoietic stem cells (BM and cord blood SC). Perspectively, such studies aim to explore the influence of TLR stimulation on the biology of stem cell niches, its influence on SC engraftment and function. Overall, the research topics are interesting and scientifically as well as clinically relevant. Yet, asymmetric cell division is currently one of the “hot” topics in SC research and thus very competitive while the focus on MSC instead of hematopoietic stem cells diminishs the attractiveness of this research plan. Considering the competition in the field and the limited research resources of the group, a more precise focus on individual projects might be beneficial rather than the broad spectrum of research topics outlined in the application and during the on site visit. It would be of particular importance to focus on the strengths of the institution (e.g. large cord blood bank) and to accompany the clinical program with appropriate basic research projects.

MSC are currently not applied clinically for the treatment of GVHD in Paris and their role in shaping a stem cell niche, though per se interesting, does not seem to fit perfectly to the other INSERM projects. Nevertheless, the PI previously showed his expertise in basic research and convinced the reviewers at the on site visit of his committment.

The role of the PI heading the immunogenetics laboratory in Hospital Saint-Louis in these projects seems to be one of general support and is not clear neither whether there is a specific research project of this component of the team.

As a general conclusion, although the past collaborations of the different partners of this team in the past was shown to be succesful, particularlly in clinical research programs, their research projects could be better and integrated within the team and in the INSERM unit. Project 2 should be more focused.

Conclusion

- Strengths and opportunities:

The team members have an excellent track record in their respective research fields and are highly qualified to perform the suggested research projects. They are nationally and internationally visible and recognized.

The research projects are scientifically sound and probably clinically relevant.

There is an excellent cooperation between clinical partners, clinical and GMP laboratories and tissue banking facilities.

The large number of transplants performed in the institution permits the conduction of informative translational clinical trials and requires a strong research environment.

The PIs of team 3 lack adequate basic research facilities and staff (particullarly the team leader), a situation that must be improved by the provision of laboratory space and basic research positions (senior researcher, post-doctorants and/or PhD student postions, technicians).

Thus far, no animal models for BMT, GVHD and tolerance are established and little laboratory work to perform mechanistic studies on the role of cells or molecules that could be found.

Improvements in platform technologies would be beneficial (e.g. 2-photon microscopy).

Collaboration on research programs (and not only clinical activity) among the researchers of the team should be strenghen.

Collaboration with the other INSERM teams could be intensified and regular lab meetings of the whole consortium should be organized, eventually also a yearly retreat.

Improved support for biobanking and biostatistics is necessary.

The work plan of some subprojects within team 3 could be more focused and better adjusted to the clinical program and the overall goals of the INSERM unit.

- Recommendations:

A strong recommendation is to recruit experienced basic scientists, trained post-doctorants, PhD students and technicians to enhance the research environment and to establish experimental GVHD models and to perform translational mechanistic studies.

The team has to intensify synergies and collaborations between projects of the team and with other teams of the unit.

The team has to gain better acces to general research infrastructures like animal facilities, imaging facilities.

Effort has to be made to gain better support on biobanking, clinical data bases and biostatistics.

5 • Conduct of the visit

Visit date:

Start: Monday 28 january 2013 at 9:00

End: Monday 28 january 2013 at 18:30

Visit site: Institut Universitaire d'hématologie, Hospital Saint Louis

Institution: IUH, Paris 7 University

Address: Rue Claude Vellefaux, Paris

Conduct or programme of visit:

9 h 00 - 9h15	AERES representative: the role and procedures of AERES
9 h 15 – 9 h 45	Director of the unit: Presentation of the past activities and project
9 h 45 – 10 h 55	Lymphocyte differentiation and homeostasis in allo- and autoimmunity Team leader Mr Antoine TOUBERT
10 h 55- 11 h 10 coffee break	
11 h 10- 12h05 Team 2	Regulation of allogeneic immune responses in renal transplantation Team leader Ms Nuala MOONEY
12 h 05 – 13h 00 Team 3	Hematopoietic stem cell transplantation Team leader Mr Gérard SOCIÉ
13h-14h lunch	
14 h 00 - 14 h 45	Parallel meetings with personnel: Discussions with engineers, technicians, administrative Discussions with staff scientists Discussions with students and post-docs
14 h 45 – 15 h coffee break	
15 h 00 – 15 h 30	Discussion with the representatives of the managing bodies
15 h 30 – 15 h 55	Discussion with the head of the unit
15 h 55 - 18h 30	Private meeting of the visiting committee
18h30	End of the visit

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

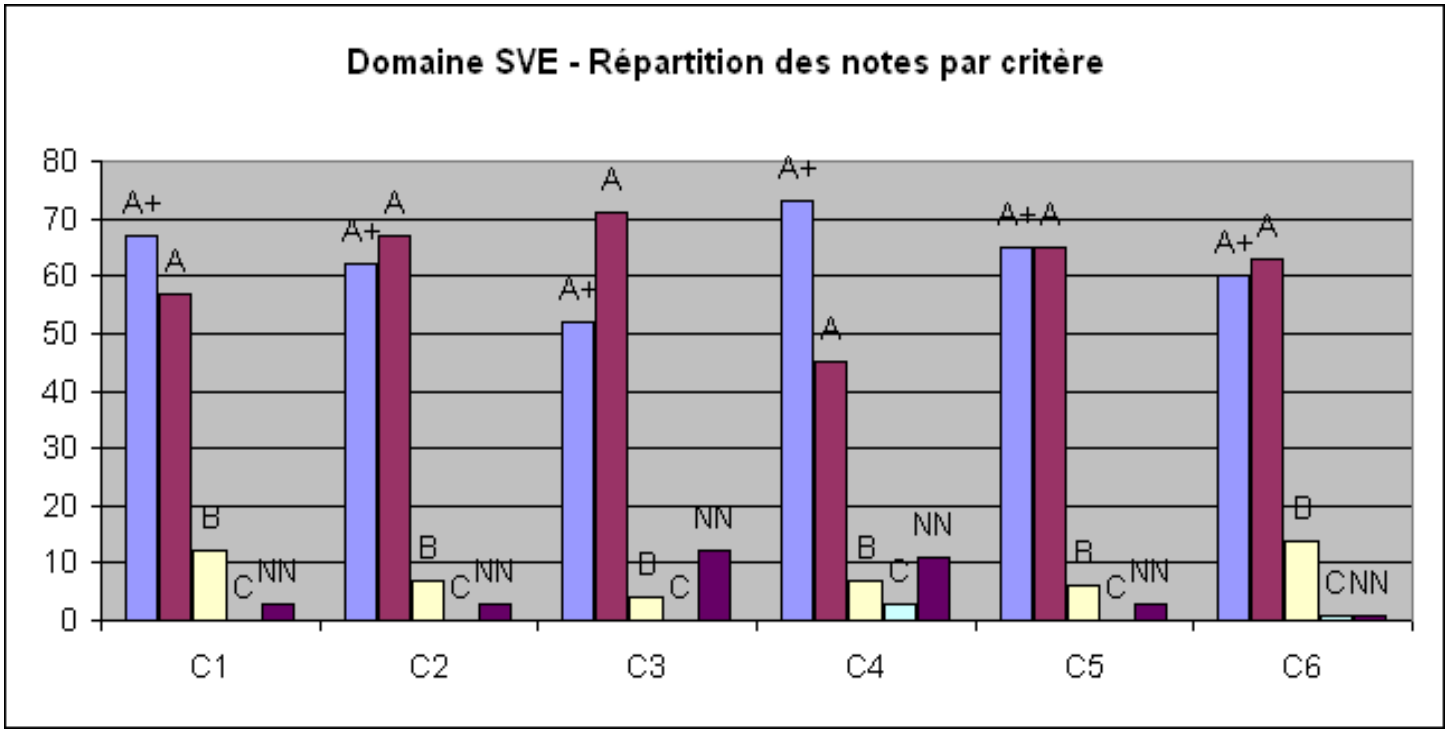
Grades

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

université PARIS DIDEROT PARIS 7

Le Président

P/VB/LB/NC/YM – 2013 - 086
Paris, le 22 avril 2013

M. Pierre Glaudes
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

S2PUR140006427 - Alloimmunité-Autoimmunité-Transplantation - A2T - 0751723R

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport d'évaluation concernant le laboratoire « Alloimmunity-Autoimmunity-Transplantation » et je tiens à remercier les membres du comité de visite pour les remarques et propositions constructives formulées et appréciées par le porteur du projet et directeur de l'unité.

Le comité mentionne à juste titre l'intérêt scientifique du regroupement de ces deux unités, qui leur donne une cohérence et une visibilité accrue sur le champ de la transplantation des cellules hématopoïétiques et du rein. Je ne doute pas que la création de cette nouvelle unité permettra une attractivité plus importante à la fois pour les chercheur.e.s et les post-doctorant.e.s, accroissant une réputation déjà forte, soulignée par le comité. Je ne peux que me réjouir de cette collaboration confirmée avec l'INSERM.

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

Vincent Berger

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(Directeur : Pr. D. Charron)

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Pr. A. Toubert
Professeur des Universités
Praticien Hospitalier

Paris, le 5 Avril 2013

Réponses au rapport d'évaluation du comité AERES de la demande de création d'unité mixte INSERM/Université Paris Diderot
« Alloimmunité-Autoimmunité-Transplantation »

Volet Général

Le comité d'évaluation a effectué un travail de grande qualité pour prendre en compte les différents aspects de la demande de création d'unité, aussi bien d'ordre scientifique que stratégique dans son intégration au site hospitalo-universitaire du Groupe Hospitalier Saint-Louis/Lariboisière/Fernand Widal et à l'IUH.

Il n'y a donc pas d'observation générale à apporter au rapport.

Antoine TOUBERT