Immunointervention dans les allo et xénotransplantations

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Immuno-intervention in allo and xenotransplantation

From the

Université de Nantes

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

February 2011

Research Unit

Name of the research unit: Immuno-intervention in allo and xenotransplantation

Requested label: UMR_S INSERM, UMR CNRS

N° in the case of renewal: UMR_S 643

Name of the director: M. Ignacio ANEGON

Members of the review committee

Committee chairman

M. Roland LIBLAU, Université Toulouse 3, Toulouse

Other committee members

M. Herman WALDMANN, Oxford University, UK

Ms. Nathalie CHAPUT, Institut Gustave Roussy, Villejuif

Ms. Clotilde THERY, Institut Curie, Paris

Ms. Veronique FREMEAUX-BACCHI, Paris

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Observers

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Report

1 • Introduction

- **Date and execution of the visit**

The site visit took place over one day and a half on February 14th and 15th, 2011. The organization allowed the visit to go smoothly. The visit started by an overall presentation of the structure and scientific goals of the Laboratory by the Director. Then, each team had about one hour to describe their achievements and projects. The committee had enough time to listen to the presentations, discuss their scientific content and to evaluate the research of each of the 6 Teams. Further, the committee had a chance to meet and discuss quite in-depth with each staff category. In addition, discussions with the students around their posters and in a more informal manner could take place. At the end, the review panel met to exchange their views and to organize the preparation of the final report.

- **History and geographical localization of the research unit, and brief presentation of its field and scientific activities**

The Unit is located over 3000 m2 in the Nantes university hospital in the same building as the Clinical immunology, Nephrology and Urology departments (ITUN). Most core technological platforms, in particular the two animal houses, are in close proximity. Both this Inserm unit and the ITUN have been at the initiation of the Nantes IHU project that, although not among the six most successful projects, has been selected for funding.

The common theme of the unit is the immunology of allo and xeno-transplantation. More specifically, the shared scientific interests revolve around the study of the mechanisms of allograft tolerance, identification of biomarkers associated with allograft acceptance/rejection, the immunological bases of chronic allograft dysfunction, the immunological effectors of kidney diseases leading to transplantation, and xenotransplantation.

- **Management team**

The unit is directed by Ignacio ANEGON. The Director meets on a weekly basis with the Team leaders and the laboratory manager and the grant manager to deal with managerial, logistics, financial and scientific issues. A formal Laboratory council gathering all the members of the unit meets every 3 months. An international scientific advisory board has been in place for quite some time. It gathers 4 renowned scientists from the USA, UK, Spain and Germany who provide recommandations following a site visit (the last one took place in June 2010).

- **Staff members**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	12	12
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	13	16
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	7	7
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	19,2	19,3
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	15,5	17,5
N6: Number of Ph.D. students (Form 2.7 of the application file)	10	15
N7: Number of staff members with a HDR or a similar grade	23	26

2 • Overall appreciation on the research unit

- **Summary**

The research unit entitled "Transplantation immunology and immuno intervention" is composed of 6 teams and 11 platforms. Two teams (Team 2 and 5) will be reorganized. Thus, scientists with expertise in hepatology and gene therapy will join Team 2, and Team 5 will be created by merging experts in the field of endothelial cells in transplantation with others having expertise in the immunological bases of kidney diseases. Of note, a new platform on ES and iPS cells will be created soon. Some projects are high ranking; others may appear more risky. The fact that the unit is well managed, dynamic, and well founded provides room for some risk taking.

The overall productivity of the unit is very good, its funding impressive (in a positive way), and its national and international visibity very strong. Taking advantage of their localization on a University Hospital campus, the unit invests strongly in translational biomedical projects and has clear recognition in this field. However, importantly basic projects are also well conducted with some reaching a very good scientific level.

- **Strengths and opportunities**

- Very strong expertise in the field of transplantation and immune intervention.

- The publication record of the unit is overall very good. A number of papers have been published in high impact journals such as Journal of Clinical Investigation, PNAS (USA), Blood, etc.

- Excellent financial support from competitive funding sources such as EU grants, ANR, PHRC.

- Dynamic, creative and efficient management of the unit by the past and current directors.

The very significant number of common core facilities that are in place to guarantee the development of many of the projects proposed.

- Good interactions between the different teams, between the teams and the plateforms, and between researchers from research organizations and clinicians.

- The close interaction with the clinical centers in the hospital is a major strength in terms of development of clinical translational programs.

- Good attractiveness and ability to recruit young and promising French researchers.

- **Weaknesses and threats**

- Some teams presented too many projects, and some of them may be risky.

- Some teams appear somewhat vulnerable despite good funding, and will require particular attention from the director.

- Some projects such as the search for new markers involved in tolerance could be intensified, although success in this aim is not guaranteed, without a deeper understanding of the underlying biology.

- **Recommendations to the head of the research unit**

- Make additional efforts to attract young research fellows from abroad.

- Give particular attention to some teams that has been recently reorganized or may be more fragile due to the novelty and the risk of some projects.

- Brainstorm with the team leaders to help reduce the number of projects developped and concentrate on the more original and/or promising research avenues. In that respect, an in-depth evaluation of the pros and cons of the xenograft program should be carried out taking into consideration the recent advances in the field and in the unit.

- **Production results**

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	12
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	13
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	1
A4: Number of HDR granted during the past 4 years	4
A5: Number of PhD granted during the past 4 years	40

3 • Specific comments

The research unit is a middle-sized biomedical research institute including mostly teams centered around the immunobiology of transplantation and immunotherapy.

This research unit was initially founded by Jean-Paul Soulillou and has become over the years a leading one in Europe in the field of allo and xeno-transplantation. The scientists from this unit organize the yearly international NAT meeting, which has gained international recognition and at the same time reflects back positively on the unit itself.

The structure is stable, attractive to new scientists and highly productive. The number of publications per year over the last 5 years ranges from 31 to 55. Half of the publications in peer-reviewed journals are in journals with an impact factor > 4. Based on the past results, the publication record and visibility, the relevance and the impact of the projects presented, the committee scored 4 out of the 6 teams as excellent or very good. The publication record of these teams is of high standard and, perhaps more importantly, some of these published data represent original and are regarded as important contributions to the field.

Given the 'biomedical'-orientation of the research unit and its location in a clinical setting, it is important to highlight that a great deal of energy was devoted to establish successful translational projects going back and forth from bedside to bench to bedside.

The vitality of this research structure is obvious and much credit has to be given to the director who has maintained and developped a setting favourable to the development of ambitious translational research programs.

The remarkable success in raising funds allows the different groups to tackle ambitious scientific and medical questions, to develop cutting edge projects, and to implement new technical platforms.

Training has been very active in the unit and, in particular, over the last 5 years 33 PhD Thesis have been granted while an additional 24 are ongoing. 10 researchers and 5 Engineers have been recruited or attracted to the Unit since 2006.

A network of international collaborations, some of them funded by the EU, consolidate the international visibility. This international link is also attested by the Center of Excellence label given to the Unit by FOCIS. An additional success of the unit lies in its strong links with socio-economic partners, in particular biotech companies.

In conclusion the committee felt that the "Transplantation immunology and immune intervention" unit is a very good, healthy, and dynamic research center with a scientific production of international relevance and a clear thematic focus.

4 • Appreciation team by team

- **Title of the team: Biology of dendritic cells and immune tolerance**
- **Team leaders: Ms. Maria-Cristina CUTURI and M. Regis JOSIEN**
- **Staff members**

	Future	Past
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	4	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	4
N7: Number of staff members with a HDR or a similar grade	4	4

- **An assessment of the results**

The team is working in the field of dendritic cells (DC) and tolerance.

- Firstly, they have studied the biology of DC subsets and particularly the role of plasmacytoid dendritic cells to induce regulatory T cells. They have studied the role of TRANCE in the T cell/dendritic cell cross talk. From this work, five major papers have been published and two are submitted.

- The role of dendritic cells in allograft tolerance has been also studied, particularly the mechanisms associated with use of autologous dendritic cells. New immunoregulatory molecules have been characterized. These include, a role of CLEC-1, a C type lectin receptor, as well as the identification of TORID and HO-1 in the induction of tolerance. Five major papers plus 1 submitted have resulted.

- In parallel, the interaction between CMV infection and dendritic cells and particularly the role of DC-SIGN in the capture of CMV as well as the role of DC SIGN soluble isoforms during CMV infection and in the anergy of DCs have been analyzed.

- Other results emerge from studies in more translational and clinical research. Two directions are followed: the use of DC-modulators for inducing tolerance in different transplantation models; and the role and phenotypic features of dendritic cells in disease, particularly in the context of ANCA associated vasculitis.

Overall, numerous publications have been generated in good international journal such as American Journal of Transplantation, Blood, Cancer Research, Faseb J., Journal of Immunology.

The partnership within this team is strong and of good quality.

During the last 4 years, 4 M2R and 9 PhD students have been graduates, 3 PhD are in progress.

- **Assessment of the impact, the attractiveness of the team and of the quality of its links with international, national and local partners**

The team is recognized at the national, European and international level. One of the leaders is President of CFCD (French Club on Dendritic Cells). Numerous collaborations are ongoing in France, Europe and South America, and members have diverse invitations to national, European and international conferences and symposia.

The team has been able to recruit some students and postdoctoral workers and also one permanent position at INSERM.

The team has been very successful in raising grants (European grants, ANR, ARC, Ligue, Roche Foundation, Centaure, FRM).

- **An appreciation of the strategy, management and interactions of the team**

The strategy of research and for fund raising is good. The quality, management, interactions and spirit of the team appear excellent.

- **Appreciation on the project**

The project is a logical continuation of the previous activities.

- One part is focused on the biology of DC and the identification of mechanisms associated with allograft tolerance particularly the role of CLEC-1 and TORID molecules in the process.

- Because they have characterized and produced tolerogenic DCs, one project will be to implement a clinical trial for inducing tolerance in kidney transplantation. This project is a well-planned translational research project.

- Another project is to continue to study the role of DC during CMV infection. In this setting, a 3-D culture system has been developed to study the interaction of CMV with different DC subsets.

- Finally, another project aims at studying the cytokine interleukin-22 BP and its interactions with dendritic cells particularly in ANCA-associated vasculitis.

Taking into account the excellent expertise of the team, these projects are ambitious and feasible, albeit somewhat diverse. The project on CMV although well developed is not an obvious fit to this team. The project concerning the use of dendritic cells for inducing tolerance will require continuing efforts and will need a committed contribution from the team within the cell therapy section.

- **Conclusion :**

— Summary

This team has a strong expertise in the characterization of tolerogenic DCs and the use of molecules capable of inducing tolerance in transplantation using different animal models. They have also a strong drive to take their research from bench to bedside. Although of high quality, some projects will need to gain more focus, and while others may need to take a lower priority.

The committee felt this is a very good team.

— Strengths and opportunities

Recognized expertise in dendritic cells subsets.

Excellent knowledge in the field of immune tolerance.

Good ability to raise funding.

— Weaknesses and threats

Too many projects albeit of good quality.

Some priority should be given to the most innovative and productive projects.

Some projects appear a little remote from the main expertise of the team.

— Recommendations

To focus the research on more fundamental aspects to better exploit the role of new molecules involved in the induction of tolerance, and to better understanding the mechanisms involved in the tolerance induced by dendritic cells. Studies with interleukin 22 BP should be developed.

- **Title of the team: Immunoregulation in organ transplantation**
- **Team leader: M. Ignacio ANEGON**
- **Staff members**

	Future	Past
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	5	5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4	4
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	4
N7: Number of staff members with a HDR or a similar grade	1	1

- **An evaluation of the productivity**

The team has developed a unique expertise on generation of transgenic and, more recently, gene-KO rats using zinc finger nucleases. In the past 5 years, they have been at the leading edge of this technology. They have generated a number of transgenic rats, and one gene KO strain, which have proven useful for a range of mesenchymal stem cells, gene-therapy and xenotransplantation studies.

Another project developed in this team is to analyze tolerogenic mechanisms during transplantation, especially the role of CD8+ regulatory T cells and of DCs, and of the activity of heme oxygenase I (HO-I) in tissue protection. Here also, the team has successfully developed a number of original projects: for example, they are one of the few laboratories to be studying the action of CD8+ Tregs.

Altogether the overall rate of publication is very good.

- **An assessment of the impact, the attractiveness of the team and of the quality of its links with international, national and local partners**

The team leader was an active participant in an international collaboration worldwide establishing the zinc-finger-based gene KO technology in the rat (one Science paper in 2009), has edited several books or issues for international publications ("Methods in Molecular Biology" and "Current Gene therapy"), has been committee member and/or co-organizer of several European or international scientific societies and meetings on transplantation, and serves on the editorial board of several journals: he clearly has good international visibility.

The team has hosted many international students and one post-doctoral researcher for short training periods. Currently, only one French post–doctoral fellow is working within the Team. With the emergence of the new gene knockout technology, the attractiveness for foreign students and post-doctoral workers is likely to be much greater.

The team leader is also member of several local committees and has established partnerships with several biotech companies, enabling the transfer of expertise and technology (genOway,Hycult), as well as a IBiSA platform able to provide a real service to other laboratories.

Local and national collaborations are well developed.

- **Comments on the strategy, management and interactions within the team**

The way the team is managed and the interactions between team members are excellent.

The productivity is very good, with one or two articles per year (or even 5 in 2010) in international transplantation or immunology journals (impact factors 3-6), plus one article in a very strong journal in 2007 (J Clin Invest, IF 16,8) and in 2009 (collaborative work on technology of KO rats, Science, IF 28).

- **An evaluation of the project areas**

Three principle projects which are currently pursued are: (1) development of genetic modifications in rats and application to other animal models (e.g., pig); (2) prevention of immunogenicity to therapeutic genes and the optimisation of pre-clinical gene therapy treatments in inherited liver diseases; (3) analysis of regulatory CD8+ T cells at the functional and biochemical level, especially in transplantation models.

The three projects are well structured, each under the supervision of distinct group leaders and two of whom are young scientists recently appointed into full time research positions at INSERM. The expertise of each group leader in their specific area is very good, and the projects are well designed and planned.

There was however some discussion amongst the reviewers that the structural work associated with TCR-peptide-MHC interactions, although technically elegant, may be delaying the studies needed to understand the mechanisms of suppression.

There was also enthusiasm amongst the reviewers for the team to exploit the use of the gene-modified rat technology for development of conditional KO rats, shown feasible by the success of the pioneering zinc-finger nuclease studies.

- **Conclusion :**

— Summary

The committee felt this is a very good team.

— Strengths and opportunities

The team is well integrated within the unit.

The team has a very strong and unique expertise in transgenic and KO rat technology, and in rodent transplant biology.

The team has 2 other ambitious projects (CD8+ T regs, and gene therapy in genetic liver diseases), which can benefit enormously from the successes of the other projects, and from the transgenic rat technology.

— Weaknesses and threats

It might be useful for the team to evaluate which directions will be the most productive for the very interesting Treg project, with the possibility of giving more focus to the mechanistic studies.

— Recommendations

We consider this to be an effective team likely to make important contributions in their 3 distinct arenas of research.

- **Title of the team : Costimulation blockade and animal models**
- **Team leaders: M. G. BLANCHO, M. B. VANHOVE**
- **Staff members**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	4*
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	2
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2	3
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	4
N7: Number of staff members with a HDR or a similar grade	3	3

* 2 PU-PH, 1 MCU-PH and 1 CCA (0.25 FTE; “Chef de Clinique Assistant”)

- **Appreciation on the results**

The overall main objective of the team is to develop novel therapies of costimulation blockade to be able to get rid of immunosuppressive drugs with strong side-effects in organ-transplanted patients, such as calcineurin inhibitors. This is a long-term goal of the team which was initiated in 2002. The major approach is CD28 blockade using an innovative agent produced by the team, sc28AT, a chimeric human/primate monovalent fusion antibody which competes with CD80/86 for binding to CD28. This reagent has the major advantage to be devoided of superagonistic activity because it cannot induce CD28 receptor cross-linking. It also preserves CTLA-4-dependent immune regulation. This is an extremely promising approach with potential high medical impact. It is also an example of public/private partnership as the development and valorization of the drug is carried out in collaboration with a biotech company (TcL-pharma).

Other research topics studied during the past 4 years include :

- LAG-3 as a target of activated alloreactive T-cells in organ transplantation. This topic has been developed in a rat model after having produced LAG-3-specific antibodies (patended by INSERM and licensed by Immutep, a biotech

company devoted to LAG-3). However, this approach may also deplete regulatory T-cells expressing LAG-3 thus preventing tolerance induction.

- Acute vascular rejection in a baboon model, targeting the classical complement pathway by using a recombinant human C1inhibitor (rhC1INH) in collaboration with the Pharming company (Netherlands) which developed the molecule and allowed its use in novel models of presensitized pig and baboon allograft recipients. This is part of the XENOME FP6 European project.

- Related to the previous topic, one co-leader of the team is coordinating the LGA platform (Laboratoire Grands Animaux), which has been essential in the development of pre-clinical models for allo and xenotransplantation projects. The laboratory fulfills all requirements in terms of operating procedures and ethical rules and will soon apply to an IBiSA accreditation.

There is an excellent publication record and many communications and awards showing an high visibility of the team, both nationally and internationally. Namely, in the past 4 years, the team published 11 original publications with one of the 2 group leaders as last co-author, including 2 publications in J. Immunol. and one publication in Science Translational Medicine in 2010 (Poirier et al.). This last publication is considered very important in the field with numerous (40) press releases. They have been associated to 17 other publications as collaborators mostly with other teams of the unit. 5 patents have been filed, 4 of which have been licensed to biotech companies (IMMUTEP, Paris and TcL Pharma, Nantes).

Partnership is strong, this team is very well integrated within the unit and developped numerous collaborations trough the LGA platform and the FP6 XENOME project. 3 PhD are underway, one post-doc is currently in the team. There is a good technical staff with 5 technicians or engineers, 2 holding permanent positions.

- **Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners**

Visibility of the team is very good at the national and international level. One of the team leaders is presently Director of the ITUN in Nantes (Institut de Transplantation-Urologie-Néphrologie). He is a member of the board of the Faculty of Medicine council, of the Société Française de Transplatation and of the ASSIM (Association des enseignants en Immunologie). As a Professor of Immunology at the Faculty of Medicine he has teaching duties and coordinates Immunopathology teaching modules. One of the team leader is Director of Research at CNRS but also has teaching duties. He received an FRM (Fondation pour la Recherche Médicale) award in 2008. Among international symposia and conferences, one team member has been consultant for WHO regulatory requirements for Xenotransplantation (Changsha, 2008). One tema member gave a lecture at the American Society of Transplantation meeting (Miami FL, 2008) at the New key Opinion leader meeting of the Transplantation Society (Cape Town, SA, 2007). Currently there is one very productive post-doctoral fellow in the team and 3 PhD. Attractiveness can be assessed as good but could be improved in the future.

The capacity to raise funds is very good with an extensive list of grants obtained during the past 4 years, including 3 ANR grants, 2 for CD28 blockade proof of concept and develoment in 2005 and 2010 and one for LAG-3 targeting in 2008. Grants were also obtained from Agence de la Biomédecine (2006), association vaincre la mucoviscidose (2010), DHOS INSERM (2009) and FP6 EU program XENOME (2008-2012). Funding from the Centaure foundation, TcL Pharma, Immutep and ROTRF have also been obtained, essentially on the anti-CD28 project. The team is also leader in an FP7 application presently under evaluation, TRIAD (Tolerance Restoration in Autoimmune Diseases).

On of the team leaders is co-founder of TcL Pharma, a biotech company created in 2007 with currently 9 employees.

- **Appreciation on the strategy, management and life of the team**

The management is very good and could be viewed as an example of co-leadership between a basic scientist and a clinical immunologist. This may be considered pivotal in the success of the team towards development of innovative therapies. The emergence of cutting edge projects is clearly apparent and evidenced by the success in getting competitive grant applications (3 ANR grants within the past 4 years, DHOS-INSERM 2009).

Both co-leaders actively participate to teaching at master (Nantes, Paris) and PhD levels. On of them participates annually to the HESPERIS European course.

- **Appreciation on the project**

Different projects have been presented by the team leaders, in line with their previous activities.

- the CD28 antagonist project was especially developed and is the main focus of the team. The team showed that sc28AT, a monovalent CD28-specific antibody, not only inhibits T effector cell activation but also increased Treg suppression in vivo. This effect was explained by a CTLA-4 dependent inhibition of Teff-APC contact while Treg-APC interactions were preserved. In collaboration with Maryland University, the team showed a preclinical efficiency of this therapy in baboons (Poirier et al., 2010). Interestingly, there was a synergistic effect between CD28 blockade and tacrolimus allowing to stop the immunosuppressive drug and inducing a state of operational tolerance. The committee was convinced by the relevance and originality of this approach. The project will be followed by :

  - improvement of the CD28 monovalent antibody through pegylation (ANR grant).
  - basic aspects to get a better understanding of the molecular mechanisms underlying the CD28 antagonist properties.
  - better define the therapeutic associations (CNI, MMF, mTor inhibitors) in the preclinical model of kidney transplantin baboons.
  - ultimately, a phase I clinical trial so that a phase I/II in kidney transplants using a GMP-grade CD28 antagonist could start in 2012.

- The other projects include :

  - LAG-3 Mabs as agonists or depleting agents of activated T cells, taking into account the concern about Treg depletion as well. A model of skin hyperesensitivity assay has been set up in primates (ANR grant).
  - Use of rhC1INH to control humoral rejection in allo and xenotransplantation (XENOME FP6 project). The concern raised by the committee on this project relates to its current relevance given the beneficial effect of the C5-specific antibody (eculizumab) already in the clinics.

The different projects seem feasible and ressources appear to the committee adequate with regard to objectives (human ressources, collaborations, grants).

— Conclusion :

This team is a leading force in the field of biotherapy using antagonists of T-cell co-stimulation in transplantation. The committee was impressed by the work achieved and by the innovative and very promising approach using CD28 antagonists in transplantation. The publication record of the team is of international standard. In addition, the team leaders were able to establish national and international collaborations with excellent teams to implement their research.

The committee felt this is a very good team with an excellent development to the clinic.

— Strengths and opportunities

Excellent interactions from basic science to translational research and ultimately to the develoment of therapies with a major medical impact in transplantation.

Quality of management.

Excellent success in grant applications.

— Weaknesses and threats

The projects involving the use of rhC1INH to prevent humoral rejection and the one investigating the therapeutic potential of LAG-3 targeting were found to be less promising. A brain storming on the rationale and feasibility of such transfer in the clinic as they were presented should be initiated.

— Recommendations

The recommendation was to put priority on the CD28 antagonist program and to build as much as possible mechanistic and basic research on it.

- **Title of the team : Immune reaction in allo-response tolerance/chronic rejection and in autoimmune-response/Multiple sclerosis"**

- **Team leaders: S. BROUARD / D. LAPLAUD**

Team 4 is focused on two main immunological topics related to allo-response tolerance in the context of chronic rejection and to autoimmune response specifically involved in multiple sclerosis. The team leader is mainly implicated in the first research program and has a smaller leading contribution in the second new research axis, which benefits of the competence of physician-scientist. The interaction between the two groups is based on use of similar experimental approaches on the role of B and CD8 T cells in the two main pathologies analyzed.

- **Staff members**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	6
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2	3
N6: Number of Ph.D. students (Form 2.7 of the application file)	8	6
N7: Number of staff members with a HDR or a similar grade	4	6

- **Appreciation on the results**

This is a large team within the INSERM U643 laboratory. It evolved from the original team towards 2 main translational research topics :

- lymphocyte regulation in tolerance and chronic graft rejection, taking advantage of the concept of operational tolerance, i.e. patients having stopped immunosuppressive treatments and with no loss of the transplanted organ. This is a rare situation in kidney transplantation. The laboratory initiated studies on the immune status (mainly B and CD8 T cell compartment) of these patients in 2004, and was a pioneer in collecting biologicals samples from these patients, having the largest collection to date (n=27). The situation of operational tolerance is much more common in liver transplantation, a topic the team began to study in collaboration with the Sanchez group in Barcelona.

- Immunopathology of Multiple Sclerosis (MS). This topic was more recently introduced in the team. Albeit the 2 topics could appear somehow disconnected, they actually share common concepts (immune regulation and tolerance, antigen specificity of allo or auto-immune responses, role of B cells in immunopathology) and common tools (T-cell repertoire analysis, functional TRAP assay).

The publication record is very good. 92 original publications with 51 papers in IF>4 journals including the best speciality journals in Transplantation and Nephrology (Am.J. Transplant., IF 6.6 ; J. Am. Soc. Nephrol., IF 7.5 ; Kidney Int., IF 6.4), Immunology (J. Immunol. ; IF 6) and Neurology (Brain, IF 9.6). There are 2 publications in high impact journals (S. Brouard et al., PNAS 2007 and L. Michel et al., JCI 2008). Subsequent dissemination of the data were done through numerous reviews and editorials (Transplant. Int. 2006 ; NEJM 2006 ; Trends Transpl. 2007 ; Front. Biosci., Nat. Clin. Pract. Nephrol. 2008 ; Transplant. Int. 2010).

Due to efficient interaction with the other teams of the unit, this team has provided some important ressources such as the DIVAT collection and database (Données Informatisées et Validées en Transplantation), which are shared with other clinical centers involved in Kidney Transplantation (Paris-Necker, Nancy, Montpellier, Toulouse, Lyon-Herriot). The DIVAT biocollection received an IBiSA national platform label.

In the context of an expert clinical research, the team has developped an excellent valorization activity leading to 6 patents since 2005 (2 of them licensed). Moreover links with biotech companies, especially TcLand, TcL-Pharma and TcL Expression, co-founded by members of the team are very tight.

- **Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners.**

The team has gained a very good visibility at the national and international levels. Three researchers joined the team between 2009 and 2011. The scientific expertise of the team leader is nationally recognized as she has been invited as a member of the INSERM CSS7. Permanent members of the team have received several awards (i.e Transplantation Society Award for "Outstanding Achievement in Transplantation Science",…) and have given invited lectures, mainly focused on transplantation and immunology, at high-level scientific meetings (ECI 2009, 13th International Congress of Immunology, 2007, World Congress of Nephrology, 2009). Moreover, the team leaders founded the world renowned and successful NAT (Nantes Actualités Transplantation) meeting. There is also a large number of publications in newspapers in the field of Transplantation and Ethics with a large audience at the regional (Ouest-France) and national level (Le Point, Le Monde, L'Expansion, …). The group working on MS immunopathogenesis is more recent but has already gained some international visibility.

The ability of this team to get funds at the local (TcLand, DRC), national (Agence de Biomédecine, Centaure, PHRC, ANR) and European (EU program "Indices of Tolerance" 2003-2008; EU program FP6 "RISET" 2005-2010) levels is excellent.

- **Appreciation on the strategy, management and life of the team**

Management of the team is very good. There is a good balance between basic and more clinically oriented research. The team appears to work smoothly. The team leaders are committed about the future of their PhD and post-doc fellows. PhD students have been successful for getting a permanent position in research, 4 in private companies and 1 in academic research as CR2 INSERM in 2010. Moreover the team attracted 2 researchers with a permanent position, including 1 CR1 INSERM and 1 DR2 INSERM.

- **Appreciation on the project**

The project is very large, patient-dependent and ambitious. It carries many excellent aspects but some others could be more challenging and risky. Overall, the balance between « low » and « high » risk projects seems good. Most of the projects appear feasible within the next 4 years to the committee, and should be productive.

Regarding the Organ Transplantation group, the committee was much impressed by the quality of the interactions between basic and applied research. Clearly this is a strength of the team, which needs to be further supported. Basic research projects focus primarily on the concept of « regulatory B cells » and their role in tolerance. Mechanistic approaches depicted are appropriate. They involve cell characterization using transcriptomics, as well as in vitro and in vivo experiments with international collaborations (for humanized mice model of human skin graft transplantation). More

applied research will include the goal to define a composite score to predict Tolerance vs. Chronic antibody-mediated rejection. Achieving this goal would be of high medical impact in patients monitoring. The score will associate molecular, histological, and clinical parameters. It has been funded by a PHRC national grant and DHOS/INSERM. It is not an easy task but, in Europe, this team is one of the very few that could achieve this goal by performing the efficient « core » association between Clinics, the DIVAT bio-bank and database, and the collaborations for microarrays and tissue array on kidney biopsies. Biostatistics will be obviously one central issue in the project.

About the Neuro-Immunology program, the main objective is to get a clue on the myelin antigens giving rise to the deleterious T-cell reactivity. Other international groups aim to identify the target antigens in the development of this disabling disease. Experimental approaches will consist of T-cell repertoire analysis using the spectratyping technique developed at TcL Expression. One original goal is to compare T cell profiles from samples obtained directly from the cerebrospinal fluid and those from peripheral blood, by using an innovative assay developed by the group: the "TRAP" (T-cell recognition of APC by Protein Transfer) assay based on the trogocytosis phenomenon to analyze T-cell reactivity against autologous APC. Issues about the role of B-cells will also be investigated in collaboration with the team leader group. This is a good example of the rationale for these 2 partners to remain associated. This project is well supported by grants and seems feasible in the coming years.

- **Conclusion :**

— Summary

The committee felt this is a very good to excellent team in many aspects. This team has a leading position at the national and international level in immunobiology of renal transplantation built on an outstanding network of collaborators, a long-term prospective biobanking and database collection (DIVAT), and an exceptional ability to raise funds and develop partnership with Biotech companies. The group working in MS immunopathology, albeit more recent, has already proven very successful.

— Recommendations

Given the visibility of the team, it could attract more post-doctoral fellows from abroad. The committee appreciates and encourages efforts made to improve mechanistic lines of research, as for instance the role of B cells in operational tolerance and the development of collaborative projects with team 2 for animal models (BANK-1, XBP-1 KO mice, CD32b transgenic rat). This is even more the case for the Neuro-Immunology projects which should be clearly hypothesis-driven and focus on MS immunopathology. Given the size of this group, the development of projects in other directions (astrocyte-lymphocyte interactions) should be discussed.

- **Title of the team: Endothelial and glomerular dysfunction: mechanisms and therapeutic targets**

- **Team leaders: Ms. Beatrice CHARREAU and M. Jacques DANTAL**

The team has been created in January 2010 and includes members from three previous teams (team 7, team 9 and 3) and a new group.

- **Staff members**

	Future	Past
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	3	3
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	3
N7: Number of staff members with a HDR or a similar grade	4	4

- **Appreciation on the results**

Several objectives of the team, in particular "mechanisms of endothelial dysfunction in Transplantation" or "characterization of anti-HLA and non HLA antibodies in the chronic kidney allograft rejection", are relevant and may be useful to the improvement of patients' treatment. Other projects relate to the pathophysiology of kidney diseases or target important translational questions.

During the last 5 years one of the Team leaders demonstrated good productivity in publications with papers appearing in good quality scientific journals (IF between 4 and 10) and in senior position (last author in J Biol Chem, 2006; Blood, 2007; Arterioscl. Throm, 2008; PloS One, 2009; Biochemical Pharmacology; 2010). Her scientific production is highly associated with endothelial cell signalling. Several publications in collaboration with other Teams from the Centre attest to the collaborative spirit. The other Team leader has published two manuscripts in a senior capacity during the last 5 years on the subject of the idiopathic nephrotic syndrome (last author in JASN, 2009 and in AJKD). The newly recruited PU-PH in Nephrology (November 2010) trained at the Centre for Complement & Inflammation Research at the Imperial College in London. Despite the short time spent in Nantes, he has recently submitted a manuscript to J Am S Nephrol on the role of Flit-1 in ANCA positive vasculitis.

Most publications of the researchers with teaching duties are clinical publications in the Journal of Nephrology.

Althogether the overall rate of publication is good.

- **Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners**

The attractiveness of the team and its international visibility could be improved, beyond the one post –doctoral fellow currently working in the Team.

Of note two past PhD students received an award from the fondation Bettencourt Schueller.

The team has won numerous institutional grants from ANR, PHRC, from Agence de la Biomedecine, and from Regional agency (Pays de la Loire) that should highten progress on all projects described. In addition, the team leader contributes to one EU-funded integrated project (Xenome).

No public-private partnership is described, but the team has submitted one patent on biomarkers of allograft rejection in 2009.

- **Appreciation on the strategy, management and life of the team**

The scientific productivity of the Team is good and reflects the capacity of the team leaders to manage their research work. Since 2006, 8 PhD Theses were defended and 4 are ongoing. The main lines of research may certainly benefit in the future from further interactions within and outside the team. A dynamic new investigator has joined the team in 2010. It is a clear ambition of the laboratory to promote nephrology as a strong domain of research. Therefore, by focusing their efforts on fewer projects the Team would be more competitive in establishing the pathophysiology of the disease processes they are investigating.

- **Appreciation on the project**

The common aim of the research in this Team is to investigate the role of antibodies and complement in nephropathies and kidney transplantation. The endothelial cells and the podocytes are the targets for the experimental part of the projects. Most projects are a continuation of previous work.

The projects investigating the mechanisms underlying endothelial dysfunction in Transplantion are well constructed and benefit from well-recognized internal expertise. The MHC class I–related chain A (MICA) molecules exist as membrane-bound and soluble isoforms and are encoded by a polymorphic gene. The project is to study the functional impact of MICA in kidney transplantation (polymorphism or isoform). Given the demonstrated importance of MICA in immune pathways, the project is of clear interest but of limited ambition. A considerable amount of research time has been invested in studies aimed at elucidating pathogenic processes that causes endothelial cell injury and ultimately bring about the biological cascade(s) that lead to the pathologic vascular changes. The team has acquired an expertise on endothelial cell signalling pathway and should take advantage of this recognized strength to reach an even higher level of scientific quality.

The team has unity in that all the PIs work on kidney diseases, but seems to target quite diverse topics. Each PU-PH works on his/her own project ie a given kidney disease or transplantation. The project aiming at better understanding the mechanisms leading to recurrence of idiopathic nephrotic syndrome is important, but could prove difficult as many molecules or cells (role of immature cells) seem to be implicated. However, no candidate markers have been identified since the first report by the group in 1998 that Protein A immunoabsorbtion improves the disease. For this project, state of the art technology will be used, and this could allow a breakthrough provided enough resources are invested. The recruitment of a full time scientist would help for the success of this competitive project. The expertise of the group in transplantation is recognized and it is important for the clinicians to demonstrate the value of the knowledge gained in biomarkers associated with kidney allograft acceptance and rejection. In that respect, a translational project on the characterisation of donor-specific antibodies (DSA) is closely linked to a clinical trial (PHRC and ANR- Emmergence bio). The project presented by the newly recruited physician-scientist stems from results obtained prior to joining the Team. His project is original and connects endothelial cell injury observed in kidney disease to VEGF and to FIt-1 activation, an endogenous inhibitor of VEGF. He also has expertise in complement and its possible role in endothelial cell activation and kidney allograft rejection.

Resources allocated to each project are reasonable, and clearly demonstrate the motivation of all members of the team to raise the necessary funds.

The scientific questions addressed by each scientist have clear clinical interest, but few novel and ambitious projects have been presented. The characterisation of molecules or cells implicated in idiopathic nephrotic syndrome is a high-risk / high-gain project, and more effort and resources could be invested in this project.

- **Conclusion:**

— Summary

The committee felt this is a good team.

— Strengths and opportunities

The team is well integrated in the unit. The PIs from this team have been able to recruit reasonable numbers of patients suffering from relevant kidney diseases. The team has a well known recognized expertise in transplantation, and has the capacity to promote clinical research at high level.

— Weaknesses and threats

Too many projects have been presented covering a large field without apparent clear prioritization. This is the likely result of the recent organization of this Team derived from 4 different Laboratories, but should now be corrected.

— Recommendations

The aims of the research are highly guided by the specialization of the different PIs. However, the Team leaders should make all efforts to maximize those interactions.

Some of the seemingly outlier projects could be restructured to gain strength and effectiveness, so as to allow better integration of the team as a whole. Whereas the productivity is good, the Team could further increase its impact by investing in more ambitious projects. The efforts of the group for developing translational research projects should be encouraged, in particular the collection of endothelial cell cultures from transplant donors need to be further exploited.

- **Title of the team : Neuronal differentiation and neuro-immune interactions: application to intracerebral transplantation**

- **Team Leader: P. NAVEILHAN**

- **Staff members**

	Future	Past
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	3

- **An assessment of the results**

The team 6 has focused its interest on three main topics related to the evaluation of different intracerebral transplantation protocols in rodents and non-primate humans. Special attention was devoted to assess experimental approaches reducing the cell rejection in animal models of Parkinson's disease (PD). Most of the projects deal improving the efficacy of this strategy by reducing the potential deleterious immune response.

In 2011 the team was composed of at least 10 persons (3 CR1 INSERM, 1 MCU, 1 PU-PH, 1 engineer, 1 assistant engineer and 3 PhD students). Within the last two years, the team diminished in numbers due to the retirement of one Inserm DR1 and the graduation of 2 PhD students. Thus two new students should be recruited.

The work of team 6 is organized into three related but independent parts:

- The first part is dedicated to the development of appropriate protocols to graft neurons into diseased brains, with a particular attention to PD and the rescue of the degenerating dopaminergic neurons. This subject, at the interface between transplantation domain and neurosciences, is potentially high impact, but also high risk. The committee found it appropriate that such a high-risk project has been undertaken in a center with strong technological and scientific expertise in the domain of transplantation. In this fruitful scientific environment, the team has not only used existing methods, but also developed innovative tools, to evaluate therapeutic strategies in animal models of PD, including primates. The results, although short on information on fundamental mechanisms, basic approaches, showed that the strategy has promise with a convincing recovery rate of treated animals.

- The second part relies on the production of a transgenic rat model of PD by over-expressing the a-synuclein gene under the control of a dopaminergic specific promoter. The rationale of creating this rat model is that "rats infected by a-synuclein-expressing virus showed some motor impairments associated with partial dopamine neuron cell loss". In this rat model, substantial alterations of olfaction have been detected. Despite this, it has not been possible to identify strong phenotype related to the degeneration of dopaminergic neurons within the mesencephalon . This 'transgenic' project has allowed the team to raise at least two grants, but the major results of this time-consuming project have not yet been converted into a significant publication.

- The third part is a new analysis of the potentialy interesting role of immune proteins on neuronal differentiation. Expression of CD3z has been detected in neurons and a mutation of this protein was found to alter some aspects of the differentiation of cultured neurons.

During the last 4 years, the team leader has published 4 articles in a senior role (J Neurosci Res 2006, 2009 ; Diffferentiation 2006 ; Exp Neurol 2010) and 3 in penultimate position (Exp Neurol 2006, Mol Cell Biol 2008, Transplantation 2010), but the other researchers of this team have also published in first or last position (Exp Neurol 2006, Neurosci Lett 2006 ; Mol Cell Neurosci 2006 ; Mov Disord 2007 ; Mol Cell Biol 2008 ; J Cell Mol Med 2009 ; Transplantation 2010) in journals with fair IF (<5.9).

- **An assessment of the impact, the attractiveness of the team and of the quality of its links with international, national and local partners**

During the last four years, the team has established collaborations related to the analysis of animal models of PD (INRA; Nouzilly France, MIRCeb; Fontenay aux Roses, CORIT; Padova, Italy). Moreover researchers from this team participated efficiently in the FP6 program XENOME devoted to transplantation. They have obtained regular fundings through regional (Centaure, Région de Loire) or national funding agencies (AFM, France-Parkinson, Fondation de France or National Research Agency). However these longstanding international collaborations led to only limited scientific exchanges. The team has efficiently trained several Master and PhD students but no post-poctoral fellow. This last aspect appears surprising because the team has been regularly well-funded but might be explained by the lack of funding for the coming years. In addition, the team members have only participated in two international conferences, presenting just that part of their work that, it seems, will be discontinued. However some members have given several popular science seminars in France. The committee felt that the team leader should try to improve his international presence within the next four years.

- **An assessment on the strategy, management and life of the team**

Based on their previous results the team has planned to undertake three different subprojects. Two are related to PD and one to neuronal differentiation. Cross talk between research projects focusing of very different aspects of neuronal function and dysfunction might be fruitful, but the rationale of having a project related to neuronal differentiation within this team was not completely clear to the committee. It appears though, that one of the projects of the latter sub-team aims at understanding mechanisms involved in the recovery in models of PD. To achieve this ambitious goal, the team will remain stable in its complement of permanent researchers, and will recruit new Master and PhD students. Until now the team has regularly trained PhD students with publications emerging prior to their thesis defense. The permanent researchers have regularly published their results in good international journals, but probably due to the necessarily long duration of some of their readout systems, the number of high level publications are limited.

- **An assessment of the project**

The team projects were based on the three directions emerging from their earlier work. The first part of the project aims at strengthening the therapeutic strategies of PD that they already evaluated. The committee was convinced that this strategy could have some important outcomes in the near future. It seemed however, that the understanding of the molecular and cellular mechanisms involved in the recovery phase was limited. The committee recommends a deeper analysis of underlying mechanisms. With regard to the rat model of PD, it was not clear to the committee why the model had been pursued so actively, given the somewhat disappointing results. The committee recommend some prioritisation of key experiments that would allow Go/No Go decisions. The third sub-project intends to further investigate the role of 'immune' proteins in the differentiation of neurons. The committee felt that there was a need to define improved control experiments that would allow to precise localisation of these proteins, and the involvement of non-neuronal cells in the observed neuronal phenotypes. In addition, some projects of this subgroup appear a little distant from the main topic of the team. The committee recommends refinements of project choice so as to be to the central interests of the laboratory. This might allow this team to benefit from the dynamism of the whole laboratory.

- **Conclusion:**

  — Summary

The committee felt this is a good team.

— Strengths and opportunities

The subject of this team is at the interface between neuroscience and transplantation. Therefore, this team can greatly benefit from the technical and scientific expertise of the whole laboratory. The team has the skills, tools, data and man power to significantly upgrade its impact and productivity in the next years.

— Weaknesses and threats

Some sub-projects without clear rationale. Not enough investigation of the basic mechanisms.

— Recommendations

This team should strenghten its work on understanding basic mechanisms. The team should highlight key experiments that could allow Go/No Go decisions on some of the projects, and to then strengthen those projects that appear fruitful. The team leaders should enhance their international presence.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
IMMUNOINTERVENTION DANS LES ALLO ET XÉNOTRANSPLANTATIONS	**A**	**A+**	**A+**	**A+**	**A**
IMMUNOREGULATION IN TRANSPLANTATION AND GENE THERAPY [ANEGON-ANEGON]	A	A+	Non noté	A+	A+
LYMPHOCYTE REGULATION AND TOLERANCE [ANEGON-BROUARD]	A	A+	Non noté	A	A
ENDOTHELIAL AND GLOMERULAR DYSFUNCTION : MECHANISMS AND THERAPEUTIC TARGETS [ANEGON-CHARREAU-DANTAL]	A	A	Non noté	A	A
DENDRITIC AND REGULATORY CELLS IN IMMUNE TOLERANCE [ANEGON-CUTURI-JOSIEN]	A	A+	Non noté	A	A
NEURONAL DIFFERENTIATION AND NEURO-IMMUNE INTERACTIONS: APPLICATION TO INTRACEREBRAL TRANSPLANTATION [ANEGON-NAVEIHAN]	B	B	Non noté	B	B
XENOGRAFTS AND ALLOTRANSPLANTATION [ANEGON-VANHOVE-BLANCHO]	A+	A+	Non noté	A	A+

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	**42**	**5**	**20**	**26**	**36**	**59**	**5**	**17**	**29**	**239**
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

*** les résultats SVE2 ne sont pas définitifs au 06/05/2011.**

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

• SVE1 Biologie, santé
SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie
SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes
SVE1_LS3 Biologie cellulaire, Biologie du développement animal
SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie
SVE1_LS5 Neurosciences
SVE1_LS6 Immunologie, Infectiologie
SVE1_LS7 Recherche clinique, Santé publique
• SVE2 Ecologie, environnement
SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement
SVE2_LS9 Sciences et technologies du vivant, Biotechnologie
SVE2_LS3 Biologie cellulaire, Biologie du développement végétal

UNIVERSITÉ DE NANTES

PRÉSIDENCE DE L'UNIVERSITÉ
DIVISION DE LA RECHERCHE
ET DES ÉTUDES DOCTORALES

Nantes, le jeudi 21 avril 2011

REF : JG/EP - 2011 RECH N° 517
SUIVI PAR : **Jacques GIRARDEAU**
Objet : Rapport d'évaluation - S2UR120001448
IMMUNOINTERVENTION DANS LES ALLO
ET XENOTRANSPLANTATIONS - 0440984F

LE PRÉSIDENT

à

Monsieur Pierre GLORIEUX
Directeur de la section des unités de recherche
AERES

Monsieur le directeur,

Je vous prie de trouver ci-joint les observations de portée générale concernant le rapport d'évaluation de l'unité « IMMUNOINTERVENTION DANS LES ALLO ET XENOTRANSPLANTATIONS » UMR 643, dirigée par Monsieur Ignacio ANEGON, observations que j'approuve bien évidemment.

Je vous prie d'agréer, Monsieur le directeur, l'expression de mes sentiments les plus cordiaux.

Yves LECOINTE

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INSERM UMR 643 : Directeur Ignacio ANEGON
ITUN : Directeur Gilles BLANCHO

Nantes, 19-4-11

This letter answers to the main criticisms made by the AERES written report that we think may have arisen from an incomplete understanding of the projects. We would also like to stress that the visit and the AERES report were very well done, the project contains many important and useful comments that will ameliorate our projects and that even for the criticisms that we answer here may have been originated by our way of presenting the projects.

Criticism on the project of team 1, on page 8 (Appreciation of the project): "The project on CMV although well developed is not an obvious fit to this team".
We partially agree with the remark since the project on the basic aspects of CMV infection does not completely fit with the "immune tolerance" orientation of team 1 but since the point was not raised during the visit we think to help by clarifying some points. The first point to take into account is that the researcher that leads this project arrived not long ago to team 1 and time is always needed to really perfectly integrate new members. The second point may be one misunderstanding coming from the fact that the project was presented more focused on the CMV/DC interaction and the result on CMV infection and not on all the possible implications of CMV on DC biology. We think that although the project on CMV infection is really pertinent and definitely prominent to understand the basic aspects of CMV infection in transplanted patients, the effects of CMV on DCs are very well integrated with the other projects of the team. Our ongoing work describing the transcriptional modifications of DCs upon CMV infection revealed strong modulation of mRNA encoding yet unknown or unexpected host regulatory molecules by the virus. A manuscript is being finished describing the overexpression in CMV-infected DCs of a molecule involved in negatively regulating DC-T interactions. Other molecules will be explored and we want to stress that it is this part of the research project that will be strengthened in the next years.

Criticism on the project of team 6, on page 23 (An assessment of the project): "The first part of the project aims at strengthening the therapeutic strategies of PD that they already evaluated. The committee was convinced that this strategy could have some important outcomes in the near future. It seemed however, that the understanding of the molecular and cellular mechanisms involved in the recovery phase was limited".
The AERES committee has a positive view on the novel immunointervention strategies developed by our group, but the report points out a limited number of experiments focused on the mechanisms leading to functional recovery. Over the next months, we will try to improve

this aspect keeping in mind that the immune cells controlling the immune response in the CNS are hard to get, in particular in primates. To date, all our behavioral data are strengthened by post-mortem IHC analyses of animal's (primate and rat) brain. Survival assessment and phenotypic analyse of the grafted porcine neuroblasts are performed to control that functional recovery is due to cell replacement. We are also currently searching for immune cells infiltrating the graft and for anti-porcine antibodies in the blood sera of transplanted animals to evaluate impact of the immunosuppressive strategies on host immune response. Indeed, we recently initiated series of experiments to evaluate whether control of the humoral response is a prerequisite for long-term survival of xenotransplants in the brain. All these parameters will be studied following the transplantation of pig hCTLA4-Ig^+mesencephalic cells, after the grafting of purified porcine dopaminergic neuroblasts, or after induction of HO-1 expression in the striatum. Interest of hCTLA4-Ig cells and HO-1 for immunosuppressive strategies is supported by a large literature and our previous in vitro data (Martin et al., 2005; Bonnamain et al, submitted). We propose to gain a deeper understanding of their biological action in case of intracerebral transplantation by evaluating their impact on immune and neural cells in vitro. T cell suppression assay will be performed using in the rat spleen-derived T cells but we will also attempt to set up the cultures of deep cervical lymph nodes. Since astrocytes and microglial cells are strongly activated in case of brain inflammation or injury, impact of CTLA4-Ig and HO-1 on their activation state will be determined. In all the cases, production of pro/anti-inflammatory molecules will be assessed. As mentioned in the initial project, particular attention will be paid to the biological effects of CTLA4-Ig on neurons. Since CTLA4-Ig may act through the co-stimulatory molecules (CD80, CD86) or through the Fc receptors, specific experiments will be carried out to determine which parts of the molecule are responsible for the immunosuppressive and neurotrophic functions.
Finally, pilot experiments will be programmed to evaluate the feasibility of analyzing T cell repertoire alterations (Melchior et al, 2005) and the production of pro/anti-inflammatory cytokines in case of long-term survival of intracerebral xenograft.

Criticism on the project of team 6, on page 23 (An assessment of the project): " With regard to the rat model of PD, it was not clear to the committee why the model had been pursued so actively, given the somewhat disappointing results."

The project was of interest since it has been funded by two national funding agencies (Fondation de France, 100.000 euros and France Parkinson, 30.000 euros). The design was correct since the rats presented spontaneous formation of mutated α-synuclein (α-syn) aggregates in targeted rat neurons, and showed age-dependent olfactory deficits as observed in patients affected by Parkinson's disease. These observations are reported in one manuscript in preparation (Boyer et al.) and in another one accepted in Parkinson's disease (Lelan et al, 2011). The rats did not exhibit spontaneous motor deficits, but a large body of evidence indicate that exposure to pesticides is a critical parameter for the development of Parkinson's disease. Thus, the α-syn transgenic rats appear as a good model to test the combinatory influence of genetic background with epigenetic/environmental factors. For this purpose, the α-syn transgenic rats will be treated with rotenone and tested for motor deficits. If no

significant motor deficit is observed, the project will be stopped as recommended by the AERES committee.

Criticism on the project of team 6, on page 23 (An assessment of the strategy, management and life of the team): " Cross talk between research projects focusing of very different aspects of neuronal function and dysfunction might be fruitful, but the rationale of having a project related to neuronal differentiation within this team was not completely clear to the committee."

We think that studies linking neuronal differentiation and intracerebral transplantation appear are integrated and relevant to the other projects of the team. Since this point was not clearly raised by the AERES committee during the visit and possibly also we did not give a clear calendar for the projects, we think that further explanations on the rationale of such a topic are important.

Firstly, transplanting neural cells in the brain requires a deep expertise in the mechanisms of neuronal differentiation, a prerequisite for an efficient integration of grafted immature neural cells leading to potential functional recovery. Therefore, a better understanding on the basic mechanisms involved in neuronal differentiation and maturation might contribute to the improvement of the graft effectiveness. Secondly, strategies using local expression of immunregulatory molecules developed in our group might affect either positively or negatively the differentiation of grafted neuronal cells, which might impact on the outcome of the graft. For these reasons, we think that studies on the mechanisms underlying neuronal differentiation and maturation should be intricately associated to intracerebral transplantation projects.

In this line, two projects have been undertaken: one focusing on more basic mechanisms of neuronal differentiation that are regulated by CD3ζ that will be completed in approximately 18 months, and one focusing on the neurotrophic effects of a local immunosuppression involved in the recovery in models of Parkinson's disease. This later project was initiated a few months ago and will represent most of the investment for the next years.

It might be also helpful to explain the origin of the first project, focusing on basic mechanisms implying the "immune" molecule CD3ζ in neuronal differentiation. This project arises from previous studies of the team devoted in characterizing new markers for neural cells with the long term goal of sorting distinct neural cell populations for intracerebral transplantation. The finding that several "immune" molecules were expressed at the cell surface of neuronal precursors, at critical periods of their differentiation, conducted us logically to further investigate the biological significance of one of these molecules, CD3ζ, on neuronal differentiation. This project has been funded by two national grants (FRC in 2007-2008 and FRM in 2010), and have led to one paper published in 2008 in Mol Biol Cell (IF 6), one paper under favorable revision in J Neurochem (IF 4) and another paper which is

submitted at this time. The last ongoing study focusing on the role of CD3ζ on neuronal maturation and animal behavior will end in approximately 18 months.
The second project was originated from data obtained in our team showing that local application of an immunomodulatory molecule within the graft in models of Parkinson's disease induced functional recovery, along with a striking neuronal sprouting. The project aims to characterize the neurotrophic effects of this immunomodulatory molecule to better understand the mechanisms underlying the functional recovery. We feel that this project fits well with the recommendation of the committee to better analyze the molecular and cellular mechanisms involved in functional recovery following transplantation.

A final formal point, the visit took place February 14 and 15 and not 15 and 16 as stated in the first page of the report.

Yours sincerely,

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