Cellules dendritiques,immunointerventions et greffes

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Cellules Dendritiques, Immuno-modulation, et Greffes

From the

Université François Rabelais Tours

February 2011

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From the

Université François Rabelais Tours

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 : Cellules Dendritiques, Immuno-modulation, et Greffes

Requested label : EA

N° in the case of renewal

Name of the director: M. Yvon LEBRANCHU

Members of the review committee

Committee chairman

M. Vassili SOUMELIS, Institut Curie, Paris, France

Other committee members

Ms. Vily PANOUTSAKOPOULOU, Biomedical Research Foundation, Anthens, Greece

M. Renato MONTEIRO, Hôpital Bichat, Paris, France

Ms. Els GOULMY Leiden University Medical Center, The Netherlands

M. Philippe GRIMBERT, Université Paris 12, Paris, France

M. Antoine TOUBERT, Hôpital Saint-Louis, Paris, France

M. Jean-François MOREAU, Université de Bordeaux 2, Bordeaux, CNU representative

Observers

AERES scientific advisor

Ms. Ana-Maria LENNON-DUMESNIL

Report

1 • Introduction

- **Date and execution of the visit**

The visit was organized on November 30th, 2010 and lasted from 11:00 am to 5:30 pm.

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

This unit is located at the University of Tours and directed by M. Yvon Lebranchu. It was created in 2004 as a "jeune équipe" working on dendritic cells (DC) and kidney transplantation. Ms. Florence Velge-Roussel will take over the leadersheadhip of the unit in 2012.

- **Staff members**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	7	6
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1,5	1,5
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	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	6	6

2 • Overall appreciation on the research unit

- **Summary**

The unit members have built an impressive connection between clinics and basic research, given the limited resources and lack of pre-existing activity in this area. This forms a very good basis for translational research. The prospective database is a very valuable asset for local and collaborative projects.

National and international connections exist for large-scale clinical investigation studies, but are lacking for more basic research projects. There is a common will to continue improving that.

Recruitment of young researchers, including MD/PhD with integrated research background, is an important priority. The arrival of a new researcher significantly improved the research environment. There is a need to continue and improve doing basic research.

- **Strenghts and opportunities**

- Very good integration between research and clinical groups;

- Translational research unit in renal transplantation and immunology with an integrated organization between research and hospital groups;

- Interdisciplinary team from basic to clinical research;

- Prospective clinico-biological database for kidney transplant patients;

- Large DNA collection for genomic studies in renal transplantation;

- Important research contributions, for example the role of IL-2 and IFN-gamma on DC maturation;

- Original future research developments: renin-angiotensin system and immune responses;

- Importance of the questions asked in the field of basic and clinical transplantation;

- Appropriate methodologies, in particular in terms of data management and analyses;

- Good potential for growing given the environment, the expertise, and the interest.

- **Weaknesses and threats**

- Interdisciplinarity increases the difficulty of being cutting edge in all areas; from basic to clinical research;

- Small critical mass;

- Need to increase connections with expert groups, in particular in basic research;

- Low international visibility and attractiveness.

- **Recommendations**

- DC networks:

    - o Be more selective on the projects in order to work in depth molecular mechanisms;
    - o Renin angiotensin is an interesting and cutting edge area;
    - o Ischemia reperfusion injury mechanisms;

- Perform more systematic work on mechanism of IS drugs on DC and link to selective pathways;
- Develop more connections with basic researchers because of the weak environment in science and immunology;

- Genomics and biomarkers

- Establish a database, and prospective cohorts;
- Link to clinical parameters: CMV, immune reconstitution;
- Important to go towards genome-wide studies;
- Continue original study based on urine analysis and peptidomics;
- Need to reinforce data analysis;

- IS drug

- Need to be more linked to molecular mechanisms.

3 • Specific comments

• Appreciation on the results

The context motivating the initiation as well as most of the current activity of the team is the drop in long-term renal graft survival, with 50% chronic allograft dysfunction, and 50% of death from other complications, including cancer. In addition, there are a large number of side effects related to the use of immunosuppressants. Research activities were established and organized in order to improve these important aspects of renal transplantation, with potential impact on other transplantation settings and for our understanding of graft rejection and inflammation in general. Three themes were defined along those lines (1) DC, innate, and adaptive immunity, (2) Biomarkers and clinical outcomes and (3) Immunosuppressive strategies. Examples of specific questions are the impact of the allogeneic effect on graft survival, development of patient-tailored immunosuppression, better choice of immunosuppression, the role of IL-2 and IFNg on DC activation, and regulatory T cell (Treg) biology.

Research outputs: The unit has produced a significant number of publication in specialty and generalistic journals, including for 2006-2009: 90 papers, among which 24>5 IF. An important output is the prospective database gathering data starting from 1985, and combining immunological, biochemical, and clinical information in order to answer relevant physiopathology and clinical questions. The unit also has an important DNA collection (1500 samples).

• Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partner

Unit members are part of various collaborative networks: French network on renal transplant, DNA collection network, Regional cluster on infection and immunotherapy, LabEx project: Therapeutic antibodies; CHU Tours: Inflammatory responses in renal physiopathology

A peculiarity of the unit is the very strong integration with the hospital and clinical teams, with many medical doctors involved in the research at various levels. Projects range from fundamental, to translational and purely clinical research, with a strength in the translational aspects.

- **Appreciation on the management and life of the research unit**

The unit hosts 6 HDR, 3 Technicians, 2 post-doctoral fellows, 5 PhD students, and a variable number of masters students. New members are expected to join, including young researchers. Staff scientists and medical doctors benefit from a good work environment, with a very good connection between research and hospital teams, including common lab meetings. Technical and administrative staff has a good degree of autonomy and is well integrated in the unit. It is actively involved in training young researchers. Students and post-doctoral fellows benefit from a good environment in terms of material, space, and financing. Following discussions with lab members, the committee had the feeling a very positive and interactive environment, encouraging exchanges and learning from others. Younger lab members were very motivated in pusruing scientific careers.

The unit is actively involved in the training of masters and PhD students, as well as in teaching. The head of the unit coordinates the DIU on clinical transplantation that he has himself initiated. He is president of the CNU commission 47-03 "Immunologie". Several unit members participate in teaching at the University of Tours.

- **Appreciation on the scientific strategy and the project**

The global strategy is well adapted to the environment and to the type of translational research performed. Azs stated above the interdisciplinarity also adds difficulty in being/remaining cutting edge in various disciplines (see above: Weaknesses and threats). The project would be strengthened by an increased focus on basic mechanisms. The critical mass in increasing, which will certainly favor this and other developments. The perspective is under discussion for applying for an Inserm unit in the near future. This would be justified by the increased size of the unit, the very good interdisciplinarity, and the good perspectives of development that would require the appropriate institutional support.

4 • Appreciation theme by theme

Theme 1:

- **3.1 General overview of the activity**

In the years 2006-2010 the team aimed at understanding certain mechanisms involved in the generation of regulatory DC and T cell subsets with the ultimate goal to translate their findings into effective and specific immune suppression during organ transplantation in patients. Their efforts have generated many publications of which some of great importance. For example, they showed that mycophenolic acid treatment of DCs renders them suppressive (J. Leukoc. Biol., 2008). They also showed that interferon-gamma licenses human DCs to induce CD8+ alloimmunity in the absence of T helper cells (*Blood*, in press). Moreover, the team demonstrated that anti-CD25 decreases the ability of human DCs to prime allogeneic CD4+ T cells (J. *Leukoc*. Biol., 2008) and that CD40 engagement on porcine DCs induces CD25 expression (*Mol*. *Immunol*. 2010). They have also demonstrated the role of probiotics in the activation of human regulatory DCs (J. *Allergy Clin*. *Immunol*., 2006 ; *Plos One*, 2008). In addition, the team has recently started a project on the role of ion channels in DC maturation and migration.

The projects were presented in a very clear way. The team proposes to continue their research efforts on the topics they have already worked trying to identify the mechanisms and to link these to the human transplantation situation. In addition, the team proposes to expand their research on the role of ion channels in DC physiology and inflammasome activation. Another researcher proposed the studies of the effects of renin receptors on DCs. They also plan to employ an ischemia reperfusion *in vivo* mouse model (that already works in their hands) to study the DC-T regulatory networks.

- **3.2 Strengths**

This is a wonderful example of academic clinicians/researchers collaborating with basic scientists in order to accomplish translational research. The topics of the proposed research are very significant for immunology and transplantation immunology and the approach is appropriate. A newresearcher, who joined in 2006, is an asset for the

team. He is a very good and rare example of a clinician with strong background in basic immunology. His expertise in studying the immune response and the DC-T crosstalk is providing the right force for the team to evolve. In fact, increasing level of publication record of the unit in the last years is noticeable. The team's proposed project on DC function and renin receptors is of high impact, novel and promising.

The leadership is excellent as also judged by their decisions on team formation and projects.

The students (Ph.D. candidates and residents) showed a very good grasp of knowledge and understanding and were characterized by great enthusiasm for their projects and their mentors. Of great importance is the fact that the students want to continue carreers in research and academia.

- **3.3 Weaknesses**

The unit lacks permanent scientists (from EPST institutes) and permanent technicians for the proposed research needs.

The team would be greatly benefited by limiting the number of projects in order to study the mechanisms involved in depth. Also, it would be important for the researchers to employ transplantation animal models to study fundamental aspects of DC and immune regulation in transplantation in vivo.

Theme 2: Genetic polymorphism and renal transplantation in Humans

Based on the clinical database and DNA collection from the cohort of renal transplant recipients followed at the Tours-François Rabelais University Hospital (Nephrology and Clinical Immunology departments), the laboratory produced already significant data using a "candidate gene" approach. Especially interesting are the impact of IL-12p40 and of PD-1 on graft survival and CMV infection published in Transplantation (2008) and J. Med. Genet. (2009). Future plans include other candidate gene (ABC transporters) approach but above all a genome-wide project. This will be made possible through a consortium bringing together 8 clinical centers in France and Belgium (notably Tours, Besançon, Bruxelles, Liège with a total of 5000 DNA samples expected). Genetic analysis will be conducted in Bruxelles.

Strong points are the quality of the clinical data collection and of the interactions with Geneticists.

Considering the fierce competition in the field, further improving collaborations at the National and European levels have been encouraged. Also adequate coding of all information facilitating future statistical analyses would secure the high value of this unique database. Focusing Genetic analysis on critical issues in Organ Transplantation, such as the occurrence of post-transplant HLA-specific antibodies, would add a significant value to the project.

Theme 3: Immunosuppressive strategies

Based on a collaborative network including many kidney transplant center, the team develops a translational original research based on analysis of different immunosuppressive strategies in kidney transplantation. Topics include several studies based on the use of inhibitors of the mTOR pathway, the characteristics of the lymphocyte recovery after the use serum antlimymphocytaire, and the analysis of the consequences of the use of Basiliximab on lymphocyte phenotype T regulatory populations. This activity has resulted over the last 4 years to 8 publications in journals with impact factor over 4. The group plans to create a multidisciplinary platform within the CHU of Tours based on the use of monoclonal antibodies in human therapy. The activity and the project are based on original and excellent operating clinical cohorts and databases even if it is essentially a clinical and translational research with few prospects more basic at the moment.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
CELLULES DENDRITIQUES,IMMUNOINTERVENTIONS ET GREFFES	A	A	A	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 FRANÇOIS - RABELAIS TOURS

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

Tours, le 22 avril 2011

SERVICE DE LA RECHERCHE ET DES ETUDES DOCTORALES

REPONSE DE L'UNITE :
CELLULES DENDRITIQUES, IMMUNOINTERVENTIONS ET GREFFES
S2UR120001554

Answer to the EARES committee

First of all, we would like to thank the committee members for their investment and their useful comments and proposals. We share the majority of your conclusions. Nevertheless we would like to comment some points regarded as a weakness in the analysis.

1 - we totally agree that the interdisciplinarity increases the difficulty of being cutting edge in all areas. Nevertheless, as underlined in the report, the very strong integration between the research team and the clinical staff of the transplant unit strengthens the translational aspect. In the future, we will be cautious to primarily develop research topics that already represent our strengths as underlined in your report.

2 - indeed the number of HDR is low, but increasing steadily in recent years (3 in 2004, 6 in 2010 and will reach 7 in September 2011). In addition, other valuable scientist have just join our team or shortly or will do it: 1) in September 2011, the team will be strengthened by the arrival of a new HDR, Dr Denis Angoulvant as professor of cardiology; he held a post-doctoral position in Toronto, and worked on ischemia reperfusion injuries and inflammation; 2) the research staff of the HLA laboratory of the "Etablissement du Sang Centre Atlantique" has recently joined our team (1 PhD and 1 research engineer); 3) two young surgeons and several young physicians are being trained in our team: we hope that some of them will be part of our team in the future.

3- we agree with the need to increase connections with expert groups, in particular in basic research, and we will do it. First, we have been co-founders - with D Abramowicz from Bruxelles - of a European network for the study of genetic polymorphism in kidney transplantation in connection with a genetic laboratory of international renown headed by Pr M Georges at Lièges. Second, we recently extended this consortium to other European centers and applied for the 2011 EDTA grant along with D. Abramowicz from Bruxelles, F. Claas from Leiden, D. Dragun from Berlin, R. Borrows from Birmingham and several other colleagues. This network aims to coordinate efforts to create large banks of biological samples backed by clinical databases to conduct

genome-wide studies in transplant patients. Finally, our team has also proposed a European network focused on “ion channels and dendritic cells” with M. Hoth, from Saarland University, A. Parekh, from Oxford and several well-known colleagues. These projects demonstrate our capacity to develop interactive connections in basic research.

4- we have been surprised that the report mentionned “a low international visibility and attractiveness”. Indeed two Brazilian professors joined our team in the last 2 years (Pr N Olsen-Camara from Sao Paulo and currently Pr M Teixeira from Bella Horizonte who has more than 300 publications referenced in Medline). The significant number of international and national invitations for academic conferences attests of our visibility within the field of transplant immunology. In addition, the head of the unit was the past president of the “Société Francophone de Transplantation”, the co-president of the last congress of the “European Society for Organ Transplantation and the president of the scientific committee of this meeting” in 2009. We therefore believe that these facts confer to our team an excellent national and a fairly good international visibility in our field of transplant immunology. Our implication as leaders in European Networks (cf 2.) will improve our international visibility.

Madame Laurence VELGE-ROUSSEL

Michel ISINGRINI
Vice-Président Recherche