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

Section des Unités de recherche

AERES report on the research unit

Pharmacologie des immunosuppresseurs et de transplantation

From the

University of Limoges

INSERM

February 2011

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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 : Pharmacologie des Immunosuppresseurs et de la transplantation

Requested label : UMR_INSERM

N° in the case of renewal : UMR_S

Name of the director : M. Pierre MARQUET

Members of the review committee

Committee chairman

M. Eric THERVET, Université Paris 5, France

Other committee members

M. Thierry DEFRANCE, University Lyon 1, France

M. Joost VAN MEERWIJK, University Toulouse 3, France

M. Thierry NAAS, CHU Bicêtre, Le Kremlin Bicêtre, France

M. Ulrich BLANK, University Paris 7, Paris, France

M. Yvon LEBRANCHU, Université de Tours, France

M. Etienne CHATELUT, Université de Toulouse 3, France

M. Alain BERDEAUX, Université Paris Est-Créteil, France, CSS representative

Observers

AERES scientific advisor :

M. Nicolas GLAICHENHAUS

University, School and Research Organization representatives

Ms. Catherine LABBÉ-JULLIÉ, INSERM

Le membre du CNU n'a pas pu se déplacer

Report

1 • Introduction

- **Date and execution of the visit**

The visit started on February 15, 2011 at 2:30 am and ended the same day at 6:00 pm. The scientific program included an overall presentation of the Unit by its Director during 30 minutes followed by three scientific presentations of the past activity and projects by three team members (30 minutes each). Meetings with PhD students, engineers technicians and administrative staff, researchers with permanent positions were also organized to discuss issues of group management.

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

The research unit is located at the Faculty of Medecine and Pharmacy, Limoges. From 2004 to 2007, this research unit was an « équipe d'acceuil ». It became an INSERM research unit in 2007. This research unit studied the pharmacology of immunosuppressive treatment used after organ transplantation, their conseqences with regards to efficacy and safety and other aspects of transplantation including anti-viral drugs. The scientific rationale relies on (1) the large variability in the outcomes of transplant patients and grafts in response to immunosuppressive drugs, (2) the absence of significant long-term survival improvement, (3) the poor selection criteria among the multiple immunosuppressive regimens, (4) the renal and cardiovacular toxicity of some of immunosuppressive drugs, and (5) the need for early biomarkers of efficacy and/or toxicity.

- **Management team**

M. Pierre MARQUET and Ms. Annick ROUSSEAU are the unit director and deputy director respectively.

- **Staff members**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	7	8
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 (Forms 2.2, 2.4 and 2.7 of the application file)	6	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	4
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	4	
N6: Number of Ph.D. students (Form 2.8 of the application file)	9	
N7: Number of staff members with a HDR or a similar grade	7	8

2 • Overall appreciation on the research unit

- **Summary**

During the past period, the group has developed original approaches in 2 fields (pharmacokinetic and pharmacogenomic). A latter topic (pharmacodynamic) has started more recently and most of the results are still preliminary. A main feature is a strict focus on their topics. Overall, the research unit has demonstrated an excellent ability to perform the analysis of data from several multicenter trials. In pharmacokinetic, they have developed valuable tools that have been transfered to the clinic for daily practice. Thank to these results and a good focus of their research in one field, they have an excellent national and international visibility within their field of research. For the future, the projects presented show the ability to promote new aspects with an original pharmacodynamic approach. Because of the large number of projects that have been presented, they should focused on some specific aspects.

- **Strengths and opportunities**

The work of the unit greatly improved the knowledge of the therapeutic drug monitoring of immunosuppressive treament and has had a successfull translation to clinic.

This was possible because of the presence of a dynamic director who has succeded in building a well focused research unit during the past 5 years. The Unit presents a very good national and international visibility and is well known in the field. This was associated with a very good management and a very good spirit. The development of pharmacokinetic model has been possible by the presence in the unit of a talented mathematician who has played a critical role in building Bayesian models. The unit has also developed strong links with local clinicians both from Limoges but also nationaly through networks of clinicians involved in transplantation and with other nationalities. They have also developed strong links with pharmaceutical companies. They benefit from a strong support from the Hospital and the University materialized by 2 Praticien Hopitalier (PH) in the unit provided and by the move in a new building in the forthcoming years, therefore allowing the members of the unit to develop new collaborations.

This has allowed an excellent scientific output for the field and for the future the development of an original pharmacodynamic approach for the future.

- **Weaknesses and threats**

The research unit does not seem to have a strategy to recruit full time researchers, i.e. researchers without teaching or clinical duties.

Beside the originality of the pharmacodynamic project, it is not clear whether the research unit will have the ressources to achieve it in all its aspects because of the relatively low number of unit members involved. For instance, the heart transplant mouse model may be difficult to implement locally.

Despite the originality of the method, the relatively low number of patients planed to be enrolled in the disease progression modeling project (pharmaco-metrics axis) may impair the results obtained.

Threats also include the dependency on external collaborations with various renal transplant centers in France and in Europe because of the relatively small number of renal transplant performed locally.

- **Recommendations**

Despite its dynamism, the sub-team working on pharmacodynamics should focus on fewer projects.

Team members working in the pharmacogenetic axis should go further to elucidate molecular mechanisms.

Team members working in the pharmacometrics axis (disease progression modeling project) should develop a strategy to enroll more patients through the collaboration with existing cohorts of patients in other centers.

Team members working in the pharmadynamics and pharmacokinetic axis should include biological agents in their study.

- **Production results**

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	7
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	0
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	88%
A4: Number of HDR granted during the past 4 years (Form 2.10 of the application file)	1
A5: Number of PhD granted during the past 4 years (Form 2.9 of the application file)	7*

* 5 declared on form 2.9 + 2 PhD theses defended at end 2010

3 • Specific comments

- **Appreciation on the results**

  — The relevance and the originality of the research, the quality and the impact of the result

The research unit pursued three main objectives.

1. Pharmacometrics of immunosuppressive drugs:

Although therapeutic drug monitoring (TDM) of immunosuppressor drugs is mandatory or consensually recommended, current limitations include (1) the fact that classical exposure indices are not relevant in all clinical situations, (2) complex pharmacokinetic profiles with delayed absorption, flat of multiple concentration peaks, and (3) the highly variable and hardly predictable overall exposure. During the past 5 years, the members of the unit have developed valuable tools that have been transfered to the clinic to improve therapeutic drug monitoring including Bayesian estimators of AUC. They have proposed a specific internet site (ABIS) which allows the clinicians to individualize immunosuppressive treatments including mycophenolate mofetil, tacrolimus and cyclosporine, which are the 3 drugs the more often used after organ transplantation. More than 9000 requests have been recorded from many transplant international centers last year.

2. Pharmacogenetics of immunosuppressive drugs:

Members of this team have studied the genetic variability of immunosuppressive drugs with regard to the pharmacokinetics/pharmacodynamics measurements and the efficacy/toxicity ratio. They have also developed during a post-doc in the US an interesting approach to clinical side effects of mycophenolate mofetil. The work involves both in vitro and clinical studies. During the past 5 years, the members of the unit did not obtain clear evidence that genetic forecasting of dose might particurlarly useful for immunosuppressor drugs (apart from CYP3A5 genotype and tacrolimus/sirolimus dosage). However, these PG-PK studies did allow the identification of critical proteins involved in immunosuppressive concentrations. This has provided candidate genes and mechanistic hypothesis involved in adverse effects of immunosuppressive drugs.

3. Pharmacodynamics of immunosuppressive drugs:

Pharmacodynamics of immunosuppressor drugs : The work during the past 5 years has focused on (1) the early screening of urinary biomarkers, (2) pharmacodynamics studies to elucidate the links between immunosuppressor drugs nocuity and graft dysfunction, and (3) graft preconditioning (FRETEP).

— The quality and the number of the publications, scientific communications, thesis and other outputs

For the past 5 years, the unit members have published a total of 94 articles in peer-review journals, among which 56 were signed by a member of the unit as first or last author. Out of these 56 papers, 12 are ranked among the top 10%. This is an excellent achievment in this field.

The unit members have a good amount (55) of international and national invitation for academic conferences.

The unit has produced 5 PhD thesis (+ 2) by the end of 2010.

— The quality and the stability of partnerships

The unit has developed stable partnerships with regional (Toulouse and Bordeaux) and national (Groupe René Spiesser) networks allowing many scientific publications. They have also developed links with internation group.

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

— The number and the reputation of the awards obtained by staff members, including invitations to international conferences and symposia

The head of the unit is president-elect of the International Association of Therapeutic Drug Monitoring and Clinical Toxicology IATDMCT, member of the editorial board of three international pharmacology journals, coordinator of drug committee of the French-speaking Society of Transplantation. Another lab member is vice-chair of the pharmacometrics committee of the IATDMCT and coordinator of the TDM committee of SFPT. Also several lab members were awarded national distinctions.

The unit members have a good amount (55) of international and national invitation for academic conferences.

The unit has organized the biannual meeting of IATDMCT in 2007.

— The ability to recruit high levels scientists, post-docs and students, and more particularly from abroad

Two foreign postdoctoral fellows and several foreign PhD students have joined the research unit during the past 5 years. A total of 14 PhD students have been trained in the lab during the past 5 years.

The implication of team members in research have allowed the attribution of a 6-month full research period for the co-director if the Unit and a hospital interface contract for 2010-2012 for another member of the unit.

— The ability to raise funds, to successfully apply for competitive funding, and to participate to scientific and industrial clusters

The unit has obtained several grants including 1 ANR as coordinator, 1 ANR as a participant, 1 grant from the Ligue Nationale Contre le Cancer (LNCC), 3 from the Limoge CHU and 2 with the company Roche Pharma.

The unit has also obtained 4 PHRC, and contracts with AFSSAPS, ABM, Ligue, VLM, CORC, Canceropole GSO, Roche, Novartis, Astellas, Wyeth, and BMS.

— The participation to international or national scientific networks, existence of stable collaborations with foreign partners

The members of the unit have developed international, national and local collaborations with several teams including with labs in Belgium, Germany, The Netherlands and Spain. Many of these collaborations have resulted in co-publications.

The unit has been involved in many clinical trials promoted by a national network of 13 renal transplant centers which have resulted in co-publications.

— The concrete results of the research activity and socio-economic partnerships

The Bayesian pharmacokinetic tools that have been developed in the research unit have been made public for clinician through a Hospital based internet site (ABIS). This has allowed many clinicians nationally and internationally to improve the care of organ transplant recipients.

Furthermore, this web site has been able to generate economic benefit for the Hospital (cotation of each patient pharmacokinetic analysis).

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

— The relevance of the research unit organization, quality of the management and of the communication policy

Seminars are organized weekly. PhD students and other lab members have also the opportunity to follow English courses every week and to attend at least one international meeting during their PhD. Most PhD students who have been trained in the lab have obtained permanent positions in the academic or the private sector. Most students who are currently in the lab are committed to pursue a career in research, either in the the academic or the private sector.

— The contribution of the research unit staff members to teaching and to the structuration of the research at the local level

The research unit belongs to the SFR superstructure and has submited a proposal to the ANR LabEx call (together with 3 other labs in Limoges).

All researchers of the unit have teaching duties and 5 out of 9 coordinate teaching programs. Unit members also actively participate to trainings organized by INSERM, other French universities, private companies, international associations.

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

— The existence, relevance and feasability of a long term (4 years) scientific project

For the next 5 years, projects will continue to focus on (1) pharmacometrics, (2) pharmacogenetics and (3) pharmacodynamics.

1. Pharmacometrics of immunosuppressive drugs:

The team will attempt (1) to generate models for population Pharmacokinetics (PK)/Pharmacodynamics (PD) and disease progression, (3) to investigate clinical outcome scores and benefit-risk ratios, (4) to study Pharmaco-Epidemiology and Pharmaco-Economics, and (5) to study resistance to, and Pharmaco-Economics of anti-Cyto Megalo Virus (CMV) drugs in transplantation.

The generation of models for PK/PD is feasible because of the tools are already developped and the presence of a talented mathematician. The disease progression model with the definition of clinical outcome score my be render more difficult because of the large numbers of variables that have to be included in the model and because the cohort of patients is relatively small (n=666).

2. Pharmacogenetics of immunosuppressive drugs:

The team will (1) perform in vitro studies to appreciate the metabolism, the transport and the cellular pharmacogenetics of immuno-suppressor drugs, (2) study clinical Pharmacogenomics (PG) and (3) pharmacogenetic-pharmacodynamic relationships. More specifically, the Polycis (POLYmorphisms of protein targets of Immuno-

Suppressants and Implication in the drug response in transplantation) will aim at identifying the most relevant polymorphisms to study, to investigate their functional consequences and to investigate their influence on immunosuppressant efficacy or toxicity in transplantation. Another project entitled PTLD (Post-Transplant Lymphoproliferative Disease) will aim at identifying the genetic polymorphisms associated with PTLD in renal transplant recipients. A larger approach to mechanistic explanation of the role of the detected polymorphisms could be of interest.

3. Pharmacodynamics of immunosuppressive drugs:

The team will study (1) immuno-suppressor nocuity, and biomarkers of renal graft lesions. Regarding the immunosuppressive drugs nocuity, they will study the nephrotoxicity and intracellular pathways including in vitro and in vivo approaches. Regarding the biomarkers of renal dysfunction, they will use targeted screening protein and peptide biomarkers in the urine and a renal tissue mass spectrometry approach (collaborations with another team).

— The existence and relevance of a policy for the allocation of ressources

The unit has increased the size of the unit staff with 7 HDR in comparison with the unit staff at its creation.

— The originality and existence of cutting edge projects

Among the projects, the disease progression modeling project and the pharmacodynamics bear a good potential and originality. The disease progression modeling project proposes an original approach with the building of non-parametric algorithms and a non-linear mixes effects models to predict the renal function deterioration. The pharmacodynamic project proposes an original approach to gain better understanding and early diagnosis of IS nocuity.

This is a sound project, logically designed and well presented. The subjects are focused even though the experimental approach is broad. The project could become of great medical relevance for the better use of the immunosuppressive drugs and understanding of their nocuities.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
PHARMACOLOGIE DES IMMUNOSUPPRESSEURS EN TRANSPLANTATION	**A**	**A**	**A**	**B**	**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**

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To the President of the AERES evaluation committee for UMR-S850 « Pharmacology of Immunosuppressive drugs and Transplantation » INSERM / Université de Limoges.

Limoges, April 11, 2011

Dear Colleague,

We acknowledge receipt of the AERES report for our unit. We would first like to thank the committee for their overall very positive comments about our report and project and their useful recommendations.

In the following pages, we have provided additional information and answers to some of the comments and recommendations made by the committee.

Best regards,

Pierre Marquet,
Director of UMR-S850 INSERM

Le Président de l'Université
Jacques FONTANILLE

UNIVERSITÉ DE LIMOGES

Answers and comments to the evaluation and recommendations of the AERES visiting committee
UMR-S850 INSERM
April 11, 2011

We thank the visiting committee for their overall very positive report about UMR-S850 INSERM.

We would like to bring additional information and answers to some of the comments and recommendations made by the committee, as follows.

1. **"The research unit does not seem to have a strategy to recruit full time researchers, i.e. researchers without teaching or clinical duties**

We agree that we should put more effort into recruiting full time researchers. However, although we have obviously not been efficient enough, we have explored several paths and made some attempts since the unit's creation in 2007:

- In 2008, we presented a candidate to the INSERM CR1 recruitment competition, Mr Torsten Böhler, who had been working on pharmacodynamic measurement of immunosuppressive effects for several years as a post-doc in a team from Toulouse with which we have a strong correlation (Dr. Nassim Kamar, at the time member of INSERM U858, Toulouse). Torsten Böhler had already been selected for an interview with the selection committee when he decided to accept a job proposed by a private company based in his home town in Germany.
- In 2009, we actively tried to convince Patrick Legembre, CR1 INSERM at the time member of UMR CNRS 5164 in Bordeaux (Pr. J.F. Moreau) and who had decided to quit, to join our unit. Patrick Legembre was during that period coordinating a research project on the non-immunological mechanism of action of mycophenolic acid, an immunosuppressant. However, he was advised by an INSERM representative to join another team in Rennes.
- In the meantime, we had posted a couple of advertisements in the INSERM weekly newsletters for tenured researchers, who may have been interested in switching units.
- We had also contacted Mr. Marc Cressan, "Mission Chercheurs" and Richard Salive, in charge of external relationships at the Department of partnerships and European relationships, at INSERM, to try and identify French researchers in foreign countries, with topics and skills compatible with our projects and who would be willing to come back to France. One of the main problems we face is that pharmacology has been disregarded as a research discipline in France for decades, resulting in very few trained scientists.
- As for the PharmDs and MDs, it is very difficult to persuade them to compete for an INSERM or a CNRS position, when they are offered higher salaries by the pharma industry or hospitals. This has been the case so far for all our PhD students with such a background, while those with a scientific background were probably not up to a position of researcher.

Despite these unsuccessful attempts, we have not given up hope and we will carry on exploring all the possibilities. Our firm goal is to enrol at least one full-time researcher during the next contract, in particular by targeting PhD students trained in our unit and accompanying them towards a future application.

2. **"Beside the originality of the pharmacodynamic project, it is not clear whether the research unit will have the resources to achieve it in all its aspects because of the relatively low number of unit members involved. For instances, the heart transplantation mouse model may be difficult to implement locally". Also, "despite its dynamism, the sub-team working on pharmacodynamics should focus on fewer projects" and "this is a sound project, logically designed and well presented. The subjects are focused, even though the experimental approach is broad. The project could become of great medical relevance for the better use of immunosuppressive drugs and understanding of their nocuities".**

We thank the committee for its positive appreciation of the scientific aspects and the clinical relevance of the pharmacodynamic projects. As far as their feasibility is concerned, we would like to put forward the following facts:

1) Exceptionally, the next "quadrennial contract" will last 6 years for the University of Limoges and the teams it hosts, so we shaped up this research axis for 6 years.
2) This means that not all the projects presented will be carried out at the same time, in parallel. We do intend to have a progressive strategy, with a sequential undertaking of the projects.
3) The Unit Council has agreed that this pharmacodynamic axis will have priority for all the future recruitments of full time researchers or teachers-researchers in the unit, as it is the newest project and a very promising one. The recruitment of full-time researchers will be a priority in the unit and we already have a few other perspectives, as two positions of MCU-PH are likely to be available within the next 4 years, one in pharmacology and one in physiology. Also, a recently recruited hospital practitioner (PH) in nephrology, Julien Allard (MD, PhD), trained in renal physiology, has expressed the wish to join our unit to collaborate with Marie Essig on her pharmacodynamic project. The reason why we didn't put these perspectives forward with the visiting committee is because they are not yet definite.
4) The pharmacodynamic axis will also have priority for the PhD and post-doc grants in our unit.

To answer more specifically on the mouse heart transplant model:

1) Rationale: if cell models are helpful to better understand the mechanisms of the IS nocuous effects, demonstrating the potential clinical relevance of such mechanisms requires evaluating them in *in vivo* transplantation models. The heterotopic heart transplantation model is one of the most easily accessible
2) The arrival of Jean-Michel Achard's group in the unit, including an experienced engineer with a long practice of vascular experimentations in rodents (James Javellaud), as well as of a technical assistant motivated to be involved in this project (Laurent Botelle) is a good opportunity to develop this model in Limoges. In particular, Jean-Michel Achard dedicates most of his working time to research, in which he has had an important personal involvement for years. This is confirmed by the quality of the publication record of his small research team over the years.
3) The feasibility of the heart transplant model itself was debated in the unit and approved owing to the encouragement of Prof. Elisabeth Cornu, PU-PH in cardiovascular surgery at CHU Limoges and who had set up and used this model in her previous works in Limoges. This decision was also made because Dr. Véronique Fauveau (Plate-forme de microchirurgie expérimentale, Institut Cochin, Paris) agreed to train Jean-Michel Achard and James Javellaud on this technique. The general opinion is that acquiring the technique does not pose particular problems, but requires a few months training from the operators before obtaining a good success rate. The time required for such a transplantation in the mouse by a trained operator is approximately 1.5 h. Once the technique has been mastered by these two permanent unit members, they will progressively involve a PhD student or a post-doc.

3. "Despite the originality of the method, the relatively low number of patients planed to be enrolled in the disease progression modelling project (pharmacometrics axis) may impair the results obtained" and "Team members working in the pharmacometrics axis (disease progression modelling project) should develop a strategy to enrol more patients through collaboration with existing cohorts of patients in other centres".

We totally agree with these comments but, as we have always done with our previous projects, we wanted first to test the pertinence of this approach before proposing it to other centres.
The PhD student working on this project under Annick Rousseau's supervision arrived in the unit on October 1st, 2010, that is 6 months before the AERES visit. In 6 months, they have been able to build up a clinical, immunological and pharmacological database of 666 kidney graft recipients at CHU Limoges (of whom more than 130 with a follow-up > 10 years), develop and compare several modelling approaches and tools and present very encouraging results in front of the visiting committee.
The strong added value of our study is that HLA antibody levels, all measured with the Luminex technique, are available for most of our patients, pre-transplantation and annually since transplantation (thanks to re-analysis of banked sera by the laboratory of immunology of CHU Limoges during the course of another thesis). However, it also means that we can only collaborate with centres where such analyses were or can be performed.
Based on our very promising preliminary results, we have now contacted Pr. Noël and Prof. Hazzan, in Lille, who have enthusiastically agreed (in writing) to collaborate to this study. They are able to provide us with more than 1000 patients, of whom at least 450 with a follow-up > 10 years, all with the

same immunological data as ours. Together, this will represent by far the largest study with such a long follow-up. In addition, we are now contacting other centres to reach a sufficient number of patients to both increase the study's statistical power and be able to validate our model in an independent cohort (see the item "external validation group" mentioned in our slide #21 presented to the committee).

4. **"Threats also include the dependency on external collaborations with various renal transplant centres in France and in Europe because of the relatively small number of renal transplant performed locally".**

In contrast to the previous points, we are reluctant to agree with this comment.
It is certainly not disputable that the renal transplantation activity is relatively limited at CHU Limoges (50 grafts/year), and that this has led us to conduct our most of our translational studies in collaboration with other French and European renal transplantation centres. The experts should however fairly recognize that we have been able to successfully conduct a certain number of such collaborative studies, and that we have now built up a collaboration network with many transplantation centres nationally and internationally. In addition, this network is not restricted to renal transplantation: the UMR-S850 INSERM made a specialty of the pharmacology of immunosuppressive drugs and has been able to set-up long-term, fruitful relationships with national and international networks of heart, liver, lung and stem cell transplantation physicians, even for transplantations not performed at CHU Limoges (e.g., lung transplantation), as well as more recently with networks of physicians involved in auto-immune diseases.
We believe that our successful building of these national and international collaborative networks, and our continuous efforts to enlarge them, indeed protect our research projects against the threat of being dependent on the local transplantation activity. We also believe that UMR-S850 is regarded as a reference for the pharmacology of IS drugs by these clinical networks, as well as by the pharmaceutical industry, though its previous achievements and its expertise in translational research in these fields.
Therefore, we would like to advocate that our ability to conduct our research within the frame of multicentre studies should be regarded as a **strength rather than a weakness**.

5. **"Team members working in the pharmacogenetics axis should go further to elucidate molecular mechanism"; and also, on page 8 : "a larger approach to mechanistic explanation of the role of the detected polymorphisms could be of interest"**

The unit has always tried (and will continue) to provide experimental data to support the clinical pharmacogenetic associations identified. For instance, one of the objectives of the ongoing POLYCIS project is to study the consequence of candidate SNPs on mRNA expression, intrinsic activity of IS target proteins, and on the inhibitory effect of the corresponding IS ex-vivo, by enzyme reaction phenotyping using human mononuclear cells collected in healthy human volunteers. Preliminary results on the mTOR protein were presented at the 14th annual meeting of the French society of pharmacology and therapeutics (2010; see reference below). This approach will be extended to the calcineurin pathway, once the pertinent polymorphisms have been identified and confirmed.

Picard N, Woillard J-B, Soudan M-C and Marquet P. Polymorphisms of the mammalian target of rapamycin (mTOR) and gene expression in the lymphocytes of healthy volunteers. 14th annual meeting of the French society of pharmacology and therapeutics, 22-25 march 2010, Bordeaux, France. 2010. **Abstract in**: Fund Clin Pharmacol: 2010, 24 (Suppl.1), p.54.

6. **"Team members working in the pharmadynamics and pharmacokinetics axes should include biological agents in their study"**

We already mentioned both in the written project and during the presentation to the committee that we were developing LC-MS/MS techniques for biological drugs, with the intention of extending our 'pharmacometrics' project to this new kind of drug. We reiterate this decision.
As for the 'pharmacodynamics' axis, we agree with the committee that biological agents will also have to be considered. However, this axis is more recent and, as highlighted by the visiting committee, has already planned quite a few new projects with more classical drugs to start with. By the way, the project on the cardiovascular side effects of conventional IS drugs will include studying angiotensin IV,

a biological agent, although still not considered as a drug. More generally, we don't think that studies of pharmacodynamic biomarkers of IS drugs have been undertaken yet, whether in France or internationally, but we agree with the committee that this will probably change over the period of the 6 years of the next contract. Therefore, we will certainly consider including other biological agents in this research.