# Tolérance immunitaire et présentation antigénique : impact en auto-immunité et en transplantation

Rapport Hcéres

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

Section des Unités de recherche

# Evaluation report

## Research unit :

## Immune tolerance and antigen presentation

## University Paris 5

December 2008

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et de l'enseignement supérieur

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## Research unit :

## Immune tolerance and antigen presentation

## University Paris 5

| Le Président de l'AERES | Section des unités de recherche |
| --- | --- |
| | *Le Directeur* |
| **Jean-François Dhainaut** | **Pierre Glorieux** |

mars 2009

# Evaluation report

## The research unit :

Name of the research unit : Immune tolerance and antigen presentation

Requested label : UMR_S INSERM

N° in case of renewal : UMR_S 580

Head of the research unit : Mr Peter VAN ENDERT

## University or school :

University Paris 5

## Other institutions and research organization:

INSERM

## Dates of the visit :

December, 2nd 2008

# Members of the visiting committee

## Chairman of the commitee :

Mrs Anne COOKE, University of Cambridge, UK

## Other committee members :

Mr Alexander CHERVONSKY, University of Chicago, USA

Mr Tim ELIOTT, University of Southampton, UK

Mrs Ana-Maria LENNON-DUMENIL, University Paris 6, France

## CNU, CoNRS, CSS INSERM, INRA, INRIA, IRD... representatives :

Mrs Elena LEVASHINA, Strasbourg, France, CSS INSERM representative

Mr Jean-François ELIAOU, Montpellier, France, CNU representative

# Observers

## AERES scientific representative:

Mr Nicolas GLAICHENHAUS

## University or school representative:

Mr Bruno VARET, University representative

Mrs Marie-Claude LABASTIE, University representative

Mr Paul KELLY, IFR representative

## Research organization representative :

Mrs Christine TUFFEREAU, INSERM representative

Mrs Annick BERTAULT, INSERM representative

# Evaluation report

## 1 • Short presentation of the research unit

- Numbers of lab members including :
  - researchers with teaching duties : 4
  - full time researchers : 4
  - PhD students : 7, all funded
  - technicians and administrative assistants : 13 including 7 with a permanent position
- Numbers of HDR and of HDR who are PhD students advisors : 4
- Numbers of PhD students who have obtained their PhD during the past 4 years : 4
- Average length of PhDs during the past 4 years : 4 years
- Numbers of "publishing" lab members : 8 out of 8

## 2 • Preparation and execution of the visit

The preparation and execution of the visit went smoothly. Enough time was given for the committee to be able to listen to the presentations, assess the research of the groups, the environment for PhD students and young research scientists as well as having time for some discussion.

## 3 • Overall appreciation of the activity of the research unit, of its links with local, national and international partners

The committee felt overall that the unit is productive, the research is of international standard and that there was evidence of established collaborative links both nationally and internationally. This was seen from the competitive grant funding already in place and that applied for as well as from the publication records.

The leader of team 2 has for many years been involved in the teaching of medical students and on Masters courses. She additionally participates in PhD thesis examinations in France as well as internationally. She has furthermore been involved in the editing of teaching textbooks. The leader of team 3 is also involved in teaching on the Immunology Masters program in the University Paris 5 and the leader of team 1 has more recently become involved in teaching undergraduate medical students and predoctoral or doctoral students enrolled in Masters or PhD progarms in the Ile de France as well as participating in PhD thesis juries. Through both teaching and research, the unit is integrated both locally and nationally. The PhD students appeared to be receiving excellent supervision and mentorship throughout their course and there was clear evidence of interaction between the young scientists in the groups.

In terms of the three research groups, it is very clear that there is good synergy between Team 1 and Team 2. Team 3 is a more recent addition to the unit and while the committee could see that there was scope for good interaction between this group and the others, this was not yet very evident. There is an anticipated move to a new building once refurbishment has been completed. This should provide a good research environment with additional possibilities for collaborative interactions.

# 4 • Specific appreciation team by team and/or project by project

**Team 1 :**

The Committee was impressed by the scientific program proposal of this team. This group has a high international standing in the field of class I antigen processing. It additionally has a strong reputation in the diabetes research field particularly in the assessment of autoreactive CD8+T cell responses. The publications from this team are of very high quality. His standing in the field is reflected in his invitations to give lectures and by his success in obtaining external grant funding from national and international sources. The future program of work builds on the findings obtained over the previous funding period.

In terms of his future program of work the committee felt that the team leader has proposed a very strong series of projects. This group discovered a new peptidase, IRAP, which may play a role in trimming of peptide precursors for cross presentation in MHC Class I. The proposed investigation of IRAP both functionally and structurally and further definition of its role in antigen cross presentation was an exceptionally strong and novel series of studies. In terms of diabetes research, the team leader has brought his expertise in antigen processing and presentation to his study of the autoantigen proinsulin (PI). Previous work from this group has shown that a targeted mutation in the insulin degrading enzyme (IDE) results in delayed diabetes onset in a spontaneous model of type 1 diabetes, the NOD mouse. This defect in IDE revealed a delay in the generation of immunodominant PI epitopes suggesting that this enzyme plays a key role in preventing central tolerance to proinsulin. The group has been given substantial funding from the Juvenile Diabetes Research Foundation to further explore this interesting project.

The other diabetes related projects described in the site visit involve the definition of autoantigenic epitopes by priming human HLA transgenic NOD mice with autoantigen fusion proteins. These autoantigen fusion proteins also have the potential to act as immunomodulators capable of inducing immune tolerance when selectively targeted to specific antigen presenting cells or when administered together with anti-CD3. Some aspects of these diabetes related projects which involve the development of assays to identify autoantigen specific T cells are already funded through the European Network. This further emphasizes the competitiveness of the work carried out by Team 1. This diabetes work nicely complements and synergises with the work carried out by Team 2. This will be further emphasized in the report on Team 2.

Team 1 has series of national and international collaborations that will further the group's research goals through provision of reagents, technical and academic input. The team leader has additionally a patent application and the potential to generate more through his future research.

**Nom de l'équipe : MHC Class I antigen presentation : mechanisms and role in autoimmune diabetes**

| Note de l'équipe | Qualité scientifique et production | Rayonnement et attractivité, intégration dans l'environnement | Stratégie, gouvernance et vie du laboratoire | Appréciation du projet |
|---|---|---|---|---|
| A+ | A+ | A+ | A+ | A+ |

## Team 2 :

The committee was impressed by the future programme of work proposed by the team leader and her team. The team leader has an excellent international reputation. She has attracted good funding for her diabetes research from national as well as international sources. In particular she has received considerable funding from the Juvenile Diabetes Research Foundation as well as from the European Union FP6. As a follow up from her pioneering work in NOD mice using anti-CD3 antibodies to reverse ongoing autoimmune destruction of the pancreatic beta cell. The team leader, together with other European colleagues, has carried out the first European clinical trial of anti-CD3 in Type 1 diabetic patients. As was also found in a North American study using a different anti-CD3 antibody this approach has shown considerable promise in a subset of diabetic patients and clearly warrants further study. Although the cytokine release resulting from anti-CD3 treatment has been markedly reduced through the use of an Fc engineered anti-CD3 there is still some cytokine release and additionally reactivation of EBV infection. To reduce the cytokine release levels further it is proposed to determine whether reduced antibody doses will achieve comparable efficacy and also, not in the written report but in the presentation to the committee, it is proposed to try combination therapy using anti-CD3 together with TNF targeted approaches. These studies can be modelled in NOD mice expressing human CD3 prior to transfer to the clinic. Importantly it might be possible in this model, in collaboration with Team 1, to selectively target islet reactive cells through the use of a novel strategy to deliver autoantigen to antigen presenting cells for T cell activation. As anti-CD3 appears to work predominantly on activated T cells this will lead to selective loss of these autoreactive T cells and permit the emergence of antigen specific regulatory T cells. This approach will also be examined in an allogeneic islet transplant setting in the human CD3 transgenic NOD mouse system.

Regulatory T cells have been shown to play a role in the immune tolerance induced by anti-CD3. A series of experiments to further explore the mechanisms underpinning their functional activity has been proposed which by using Foxp3-GFP knock-in NOD mice should enable the team leader and her group to analyse in more detail the generation, distribution and phenotype of the cells regulating autoreactivity. TGF has been shown to play a role in anti-CD3 mediated tolerance induction and while this is produced by the induced Tregs it is possible that it also comes from dendritic cells. These aspects of future studies could be enhanced by the use of confocal microscopy and collaboration with Team 3

The proposal to analyse the mechanism underpinning EBV reactivation using tonsil cells from EBV positive individuals might lead to a strategy to prevent reactivation following anti-CD3 therapy. As the clinical trials demonstrated efficacy in only patients with the highest evidence of residual beta cell function it is hypothesized that intervention in the pre-diabetic period could provide more widespread improvement. This work would be aided through analysis not only of autoantibodies but also through collaboration with Team 1 on monitoring T cell responses in the PBL of prediabetic individuals. The anti-CD3 clinical trials have been, and will continue to be, carried out through existing collaborations in Europe and using antibodies available through collaborating companies.

Team 2 has additionally been interested in the effect of infection on the development of Type 1 diabetes and has demonstrated that the bacterial product, OM-85, affects diabetes onset through interactions with TLR2 and TLR4. It is proposed to further dissect the mechanism by which diabetes prevention is obtained by using a range of knockout NOD mice and examining Treg and NKT cell function. Again there is potential for collaboration with Team 1 to determine whether there is any effect on autoreactive T cell priming following OM-85 in vivo treatment of young NOD mice.

**Nom de l'équipe : Induction and restoration of immune tolerance**

| Note de l'équipe | Qualité scientifique et production | Rayonnement et attractivité, intégration dans l'environnement | Stratégie, gouvernance et vie du laboratoire | Appréciation du projet |
|---|---|---|---|---|
| A+ | A+ | A+ | A | A+ |

**Team 3 :**

The committee appreciated that Team 3 has only recently joined the Unit and as such is at a very early stage in becoming established. While it was evident that there is a potential for collaboration with the other Teams this was not formally emphasized in the presentation by the team leader. The presentation given by the team leader to the committee was much wider in terms of its remit than that provided in the report. It was very difficult for the committee to discern the major themes from the presentation and there was concern about lack of focus. It is clear from their publication records that the two members of the team are productive and imaginative scientists and it will be very important for them in this transition phase in a new research environment that they focus down and capitalize on their existing strengths and do not dissipate their energies.

There are several considerable strengths in Teams 1 and 2 but one area which is lacking is expertise in advanced microscopy techniques which have the potential to pinpoint key cellular interactions in vitro and in vivo. This expertise is one clearly present in Team 3 and could form the basis of many fruitful interactions and collaborations.

**Nom de l'équipe : Molecular and cell biology of immune system regulation**

| Note de l'équipe | Qualité scientifique et production | Rayonnement et attractivité, intégration dans l'environnement | Stratégie, gouvernance et vie du laboratoire | Appréciation du projet |
|---|---|---|---|---|
| B | A | B | NN | B |

## 5 • Appreciation of resources and of the life of the research unit

Team 1 and 2 have been successful in bringing in external funding. While having excellent independent programmes of work, they show clear evidence of synergy and collaborative intent. They have used their resources to good effect. Team 3 is only recently established in the Unit and it is too early to see clear evidence of collaboration and synergetic interaction. It is anticipated that there will be a move to a newly refurbished building. This should be good for the Unit as it will not only provide improved research laboratory facilities but expand the potential for collaboration with other groups on site.

## 6 • Recommendations and advice

— Strengths :

The excellent track records of Team 1 and 2 in delivering results and attracting external funding coupled with their local, national and international collaborations make this a very strong Unit.

— Weaknesses :

Team 3 at the moment is just becoming established and does not have clearly defined links with the other two teams. It will be important for the leader of team 3 and his colleagues to establish a good basis for collaboration with teams 1 and 2 in addtion to those that he holds oustide the unit.

— Recommendations :

It is important that Teams 1 and 2 find sufficient funds and support to carry on their exciting and important research. It is also important for team 2 to make an effort to recruit full-time (tenure) researchers (scientists) as a disequilibrium could be observed between team 1 & 2 in terms of staff researchers.

It will also be important for Team 3 to establish good collaborative links with the other 2 teams in the Unit and additionally focus down more. It will be important for Team 3 to bring in some external funding possibly in collaboration with the other two teams.

| Note de l'unité | Qualité scientifique et production | Rayonnement et attractivité, intégration dans l'environnement | Stratégie, gouvernance et vie du laboratoire | Appréciation du projet |
|---|---|---|---|---|
| A+ | A+ | A+ | A | A |

UNIVERSITÉ
PARIS DESCARTES

*Le Président*
Axel KAHN

Paris, le 31 mars 2009

DRED 09/n°125

**Monsieur Pierre GLORIEUX**
**Directeur de la section des unités de l'AERES**
20 rue Vivienne
75002 PARIS

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport du comité de visite concernant l'unité «**UMR-S 580 Tolérance immunitaire et présentation antigénique : impact en auto-immunité et en transplantation**» rattachée à mon établissement.

Ce rapport n'appelle pas de commentaire particulier de la part de l'Université.

Je vous prie de croire, Monsieur le Directeur, à l'expression de ma meilleure considération.

Le Président de l'Université

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FACULTÉ DE MÉDECINE PARIS DESCARTES

UNIVERSITÉ PARIS DESCARTES

**INSERM U580**

*Peter van Endert, Directeur*

Paris, le 25 mars 2009

# REPONSE AU RAPPORT D'ÉVALUATION DE L'AERES SUITE A LA VISITE DE L'U580 LE 2 DECEMBRE 2008

## 2 – OBSERVATIONS GENERALES

We were delighted to learn that the committee appreciated the quality of the results, the success in attracting funding, the international standing and the collaborations of the teams and their leaders, concluding by qualifying our unit as very strong. Having by now worked for one year without secretary/accountant, we are equally pleased with the committee's recommendation to provide sufficient support to the unit.

We wish to comment on the project of team 3 which recently joined the unit. We fully agree with the two recommendations formulated by the committee, advising team 3 to establish strong collaborations with teams 1 and 2 sharing their expertise in advanced microscopy techniques, and to seek additional external funding. Regarding the former point, a collaboration with team 1, resulting in a collaborative manuscript currently in revision, has been actively pursued since 2008. An additional collaboration with team 2 concerning interactions between regulatory T cells and dendritic cells in pancreatic lymph nodes has been launched more recently, and has been included in a EC grant proposal currently under review. Team 3 is also participating in two grant proposals under review by the "Agence Nationale de Recherche". In conclusion, team 3 is already implementing the recommendations pronounced by the committee. We also wish to clarify the scientific focus of team 3, which apparently was not discerned sufficiently in the presentation by the team leader. Team 3 clearly focuses on the mechanism of action of regulatory T cells with particular emphasis on gene therapy settings, consistent with an extended and focused publication record of both tenured team 3 scientists, and invitations to international meetings and external seminars. We should also like to mention that the research program of team 3 has recently been evaluated and awarded funding by "Fondation pour la Recherche Médicale" and "Association Française contre les Myopathies".

(Peter van Endert)

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