Développement du lymphocyte normal et pathologique : transduction des voies de signalisation

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Normal and Pathological Lymphocytes and Cancer

From the

University de Picardie

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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 : "Lymphocyte normal et pathologique et Cancers"

Requested label : UMR_S INSERM

N° in the case of renewal : U925

Name of the director : M. Jean-Pierre MAROLLEAU

Members of the review committee

Committee chairman

Mrs Elizabeth MACINTYRE, Université Descartes, Paris 5

Other committee members

Mrs Hélène COPPIN, Université Paul Sabatier, Toulouse

M. David TULASNE, Université Lille 1, Lille

M. François-Loïc COSSET, Université Claude Bernard Lyon 1, Lyon

M. Patrice CACOUB, Université Pierre et Marie Curie, Paris 13

M. Jean-Pierre SAVINEAU, Université Bordeaux 2, Bordeaux

M. Jean SOULIER, Université Diderot, Paris, Inserm CSS5 and CNU representative

Observers

AERES scientific advisor :

M. David DOMBROWICZ

University, School and Research Organization representatives :

Mrs Christine TUFFEREAU, Inserm

M. Georges FAURÉ, Université de Picardie

Report

1 • Introduction

- **Date and execution of the visit**

Visit took place on February 9th, 2011. The proposed director made a general introduction on the team and the future projects that were more extensively presented by senior researchers from the team. Some posters were presented by PhD students. After close-doors meeting with the University and Inserm representatives, the committee met researchers, students and technicians in the absence of the proposed director. Evaluation ended with a closed-doors meeting of the jury.

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

The unit was created in 2003, under the direction of M. Kaiss LASSOUED and is located within the Faculty of Medecine at Amiens. Its historical interests were early B lymphoid development and signalling, prinicipally via the pre-B Cell Receptor (BCR) and via STAT5. Renewal of the unit as a single-team is requested by M. Jean-Pierre MAROLLEAU, with four projects based on analysis of normal and pathological B and T lymphocytes and their roles in lymphoid oncogenesis.

- **Management team**

The director is M. Jean-Pierre MAROLLEAU.

- **Staff members**

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	10
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 , 2.4 and 2.7 of the application file)	14
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	7
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2
N6: Number of Ph.D. students (Form 2.8 of the application file)	4
N7: Number of staff members with a HDR or a similar grade	4

2 • Overall appreciation on the research unit

- **Summary**

The historical research themes of the unit were signalling through the pre-BCR, the function and expression of ZAP70 in normal and leukemic B cells and the role of TGF-beta and STAT in precursor B cells. These were essentially led by two researchers who both left the unit in 2008. Four subsequent projects have been developed including :

- Analysis of atypical Immunoglobulin (Ig) kappa rearrangements;

- The potential role of the SLAM family CD229 receptor in Hepatitis C Viral infection of B lymphocytes;

- Analysis of the innate immunity of human Mucosal Associated Invariant T lymphocytes and their non-classical MR1 receptor;

- Assessment of the potential for reprogramming from B lymphocytes in chronic lymphocytic leukemia to plasma cells in myeloma.

The role of the past director in the proposed future program was not clear from the documents submitted for evaluation prior to the site visit and was not clarified during the visit.

- **Strenghts and opportunities**

The arrival of a PU-PH and an MCU-PH/Avenir in 2005, followed by one MCF (CNU65) in 2006 and one PU-PH and two MCU-PH in 2008 has led to a significant reinforcement of teacher-researchers in Immunology, Cell Biology, Genetics and Hematology, in compensation for the loss of the EPST researchers. The proposal to progressively identify common research themes both within the proposed research group and between neighbouring groups on the Amiens campus is to be encouraged. The functional immunological aspects of HCV infection of mature B lymphocytes, potentially in synergy with the EA4294 team is one such example. The involvement of the proposed new director in a large number of national cooperative clinical studies is likely to help progressive integration of the research teams in appropriate translational projects, as cited during the presentations of individual researchers during the visit.

- **Weaknesses and threats**

There is clearly a problem with the transmission from the previous to the proposed director. The previous 4-year mandate was presented neither by the past director nor his proposed successor and the past director was not present during the audition of tenured scientists, despite the fact that he still appears to be part of the proposed research team.

The strong local academic support for tenured posts and post-doctoral positions is out of balance with the absence of full time researchers and has not led to the attribution of competitive national funding other than one Avenir program awarded in 2007, nor to an appropriate number and level of publication. The four proposed projects have little inherent inter-relationship, as described prior to and during the site visit. In keeping with this, there is a low number of co-publications by members of the research unit.

The new director plans to play a predominantly managerial role, in keeping with significant clinical responsabilities in hematology, oncology and cell therapy, including involvement in the recently awarded EQUIPEX “FIGURES”. This may further contribute to the pre-existing dispersion, despite a very convincing desire to become involved with the unit during the presentation at the site visit.

- **Recommendations**

- The long list of manuscripts cited as being in preparation should be submitted and published.

- The role of the ex-director should be clarified.

- The unit must focalise its research themes in order to become more competitive and needs to undergo fundamental restructuring in order to ensure collaboration between the individual teacher/scientists.

- The SLAM/CD229 project, once published, should be explored in a synergic fashion with both the hematology/oncology expertise in mature B lymphoid malignancies within the unit and with the neighbouring EA4249 team.

- The atypical Ig kappa rearrangement project should be redirected from immature to mature B lymphoid malignancies, in order to reinforce the CLL/myeloma reprogramming project. There is also significant scope for use of the existing immunogenetic expertise in application to the understanding mature B lymphoid oncogenesis.

- The cell therapy background and expertise of the proposed new unit director should be considered as a potential basis for futur project development at the immunology interface. As a specific example, the MAIT project might be explored within the context of mucosal grafting. Alternatively, the role of these cells in non-malignant disorders such as rheumatoid arthritis should be explored with the relevant clinical teams on the Amiens Campus.

- **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)]	0.87
A4: Number of HDR granted during the past 4 years	2
A5: Number of PhD granted during the past 4 years	4

3 • Specific comments

- **Appreciation on the results**

In total, 17 publications are cited, of which 11 have an IF>5. Six of these were published with ex-members of the unit as first or last author (Biochem J., Haematologica, Blood, Oncogene, J. Biol.Chem) and the remaining correspond to collaborative publications in reviews with intermediate IF (Leukemia, PloS Biol, J. Immunol.).

No comment can be made on the ongoing pre-BCR and B lymphocyte signal transduction projects of Team 1, led by the previous director, since these were described exceedingly succinctly in the written documents and were not presented during the site visit.

The SLAM/CD229 and MAIT projects are promising, but the limited data presented and, particularly, published is worrying. Notably, of the four future projects presented, only one (MAIT) has benefitted from previous publication on the subject.

Four students obtained a PhD thesis during the 2007-10 period, but it is noteworthy that all four were on the STAT5 theme, which was not presented.

Two members of the group gave one invited talk each and the ex-director gave three, all at national meetings.

The aforementioned significant changes in the constitution of the unit make evidence of partnership stability a weakness rather than a strength.

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

No mention was made of invitations to international conferences or symposia.

No mention of participation to national or international networks or collaboration with foreign academic laboratories was made.

No mention was made about socio-economic partnerships.

No foreign scientist, post-doctoral researcher or student was recruited. This is clearly problematic at both the national and international level.

During 2008 and 2009 one ANR (total 60 k€) and one AVENIR (90 k€) were obtained. For 2011, only one research contract has been obtained (AOL) and two others requested. No participation to scientific or industrial clusters was mentioned in the written documents, but the cell therapy participation (not one of the cited team projects) in the EQUIPEX "FIGURES" project was mentioned during the site visit.

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

The apparent lack of transition from the past to the proposed management was striking. The proposed future management is heavily dependent on the ability of the three young MCU/MCU-PH to develop competitive research under the direction of a director with a declared coordinating role but with heavy clinical duties.

It is to be hoped that the proposed projects will lead to appropriate publications, which might make grant awards easier to obtain.

The large number of locally funded university appointments should ensure adequate availability of teachers. The cited transfer of one post-doctoral fellow (PhD obtained in the research unit) directly to DCEM3 medical training is somewhat surprising.

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

The team should concentrate their efforts on one or, maximally, two projects, based on published data. Despite the lack of publication and the succinct presentations, the panel considers that efforts should be concentrated on the MAIT/MR1 and the CD229/mature B lymphocyte projects.

Allocation of ressources will be determined by initial (CD229) or continued (MAIT) publication.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
DÉVELOPPEMENT DU LYMPHOCYTE NORMAL ET PATHOLOGIQUE : TRANSDUCTION DES VOIES DE SIGNALISATION	**B**	**A**	**Non noté**	**B**	**B**

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 Picardie
Jules Verne
www.u-picardie.fr

Amiens, le 20 avril 2011

Monsieur le Président

AERES
20 rue Vivienne
75002 PARIS

Direction de la Recherche,
de la Valorisation et de l'Innovation
Chemin du Thil
80025 AMIENS Cedex 1
☎ 03-22-82-72-40
03-22-82-79-50
e-mail : stephane.duez@u-picardie.fr

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Objet : réponse officielle évaluation LNPC – UMR S 925
Référence AERES : S2UR120001856 - Lymphocyte Normal et Pathologiques et Cancers - 0801344B

Monsieur le Président,

Je tiens tout d'abord, au nom de l'Université de Picardie Jules Verne et en particulier au nom du directeur et des membres de l'Unité de Recherche « Lymphocyte Normal et Pathologiques et Cancers » (LNPC) à vous remercier pour la qualité du rapport d'évaluation ainsi que pour les échanges constructifs que nous avons pu avoir avec le comité lors de la visite du 9 février dernier.

A la suite de la transmission du rapport d'évaluation, le Directeur, les membres de l'Unité et moi-même tenons à apporter les précisions suivantes.

1 - A sa demande, le Directeur de l'Unité au titre du précédent contrat ne fait plus partie de l'organigramme de la future unité et développera ses thématiques dans une autre structure. Afin de respecter sa décision, il apparaissait donc illégitime de présenter ses travaux sur le pré-BCR.

2 - Nous avions conscience que la dispersion sur trois axes pouvait être un handicap au projet. Nous n'avions pas exprimé clairement le resserrement à 2 thématiques prévus dans le futur de la nouvelle unité. Comme le suggèrent les experts, nous recentrerons notre activité sur :
- Les cellules MAIT/MR1,
- Les molécules SLAM/Lymphocytes B matures,

Le rôle des molécules SLAM dans la relation MAIT/Cellules présentatrices d'antigènes sera bien évidement examiné.

Nous souhaitons cependant continuer une activité de recherche translationnelle en lien avec les services cliniques d'Hématologie et d'Oncologie.

Le projet sur les réarrangements Vκ/Vκ doit prochainement aboutir. Le Docteur Brigitte GUBLER et le Professeur Jean-Pierre MAROLLEAU rejoindront les 2 groupes précédemment cités.

UNIVERSITÉ de Picardie Jules Verne

3 - Le comité a émis des réserves concernant le nouveau porteur du projet, le Professeur Jean-Pierre MAROLLEAU. Il est à préciser que son implication clinique se fait uniquement dans le domaine de l'Hématologie et de la Thérapie Cellulaire centrée sur la préparation des greffons en vue d'autogreffe et d'allogreffe.

Fort de son expérience, le nouveau Directeur de l'unité aura un rôle managérial et scientifique important et aura pour objectifs, comme nous l'avions précisé, de réorganiser l'ensemble des équipes, de redynamiser l'unité, et de veiller à une participation plus importante dans la vie de l'établissement.

4 - Nous regrettons le départ de deux chercheurs dont un EPST, ce qui a affaibli la structure et nous impose le recrutement de futurs chercheurs sur les thématiques du projet.

5 - Les articles vont être envoyés prochainement.

L'ensemble des membres de l'Unité continue à s'impliquer quotidiennement dans ce projet qu'il porte avec conviction. Ce projet a été en particulier fortement soutenu grâce à des efforts constants de l'établissement, du CHU et du Conseil Régional de Picardie.

L'existence d'une unité de recherche sur le thème proposé nous paraît très importante pour le développement du Pôle Santé au sein de l'Université Picardie Jules Verne.

Je vous prie d'agréer, Monsieur le Président, l'expression de mes sincères salutations.

Le Président de l'Université de
Picardie Jules Verne

Georges FAURÉ