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

Section des Unités de recherche

AERES report on the research unit

Immunologie et pathologie

From the

Université de Bretagne occidentale

January, 2011

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

January 2011

Research Unit

Name of the research unit: Immunologie et pathologie

Requested label: EA

N° in the case of renewal: EA 2216

Name of the director: M. Jacques-Olivier PERS

Members of the review committee

Committee chairman:

Mrs Claude-Agnès REYNAUD, Université René Descartes, Paris, France

Other committee members

M. Ralf KUPPERS, University of Duisburg-Essen, Essen, Germany

M. Olivier THAUNAT, London Research Institute, London, United-Kingdom

Mrs Marie-Christine BENE, Université de Nancy, Nancy, France, CNU member

Observers

AERES scientific advisor

M. David DOMBROWICZ

University, School and Research Organization representatives

M. Pascal GENTE, Université de Bretagne occidentale

Report

1 • Introduction

- **Date and execution of the visit**

The visit took place on January 25th, and included a three-hour presentation of past achievements presented by the former director of EA2216, followed by future projects presented by the new director and by senior scientists from the group, with each topic submitted to scientific discussion with the members of the committe. Meeting with scientists (in the absence of both the future and former directors), with the technician and with students took place before a short break devoted to discussions in front of the posters presented by the PhD students. A presentation of the local university environment was presented by university representatives (university, CHU, and Ecole doctorale).

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

The group was created in 1983 by P. YOUINOU, and, after being reconducted under various denominations as a research unit supported by the ministry of research, became EA2216 in 1992. P. YOUINOU will retire at the end of the year, and the direction will be assumed by J.O. PERS. The unit is located next to the laboratory of immunology of the Brest University Hospital (Morvan) and has developped strong links with the surrounding clinical departments of rheumatology, hematology and nephrology.

The team has developed a long-standing expertise in the field of auto-immune diseases (Sjögren syndrome, systemic lupus erythomatosus and rheumatoid arthritis), with a specific emphasis of the B-cell effector part, expertise that is translated into a considerable activity in the field of therapeutic trials, while also developing studies on normal B cell physiology. A special focus over the years has been devoted to the specific subset of CD5+ B-cells.

- **Management team**

As mentioned above, the direction of the team will change at the end of the year, a transmission that has been carefully anticipated and prepared, and appears to meet the consensual approval of all members of the team.

- **Staff members**

The structure of the team has the specific features of an Equipe d'Accueil within a University hospital, being composed of permanent members with major clinical and/or teaching duties, with no full-time scientists or post-docs. All scientists (including an engineer) have an HDR, allowing the mentoring of a large number of PhD students, who are in charge of experimental projects.

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	8	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 (Form 2.2 and 2.4 of the application file)	3	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1.5	1.5
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	8	
N7: Number of staff members with a HDR or a similar grade	8	9

2 • Overall appreciation on the research unit

- **Summary**

The team has developed a specific expertise in the identification of the role of the B cell compartment in auto-immune diseases, and in particular in Sjögren syndrome, shifting the focus towards the involvement of B-cells, besides T-cells, in the pathophysiology of the disease. Specific questions have been developed concerning the role of the BAFF survival factor in auto-immunity, of the modulation of CD5 expression according to epigenetic disregulation in Sjögren syndrome and LED. More clinically focused studies have ben designed to decipher the mechanism of action of IVIg or anti-CD20 therapies. Several of these observations appears to lead to new developments concerning the regulation of the normal B cell compartment.

This group with a long history of prominence in the landscape of Health Science in Britanny is faced with the challenge of a transition from a charismatic leadership to a new management. This has been well prepared, and all senior researchers, although none of them is full-time scientist, manage to devote a significant portion of their time to research and are assisted by a skilled and motivated group of PhD students with good coordination. Based on both fundamental and clinically-oriented research, the group's fields of interest are centered on B-cell functions but should still strenghten their focus on the most promising axes.

- **Strengths and opportunities**

Among the specific strengths of the team are the strong links established over the years with the surrounding clinical departments. They allow very efficient translational research as assessed by the numerous clinical trials and cohort studies coordinated by the team. Its deep implication in the regional teaching environment, together with strong supports from Region Ouest and from the University and University Hospital has allowed for the establishment of a consequent task force of PhD students. The group is well-structured in spite of the lack of full-time researchers. A strong international network has also been developed by the former director, which will provide good opportunities

for further cooperations and possibly post-Docs. Several very promising scientific projects rely on observations originating from the team, emphasizing the fruitful exchange between basic science and observations emanating from the study of auto-immune diseases. The next step, already quite advanced for some topics (CD5, BAFF), will obviously be to raise these observations to the level of concepts of general biological relevance.

The team will have a new director for the next 5-year term, after a previous directorship of 27 years. This transition has been carefully prepared, and the authority of the new head of the lab appears already well established and recognized. The new addition, in the team, of university-hospital professors in Nephrology and Rheumatology will strengthen the clinical input of the group's work.

- **Weaknesses and threats**

The new head of the lab will have to establish himself as a internationally recognized leader in the field in continuation with what was achieved by the former director. Whereas this could temporarily reduce the visibility of the group, the impact will obviously depend upon the quality of the science achieved, allowing the emergence of a new scientific leadership. Moreover, in the present organization of the team, the development of scientific projects relies on the sustained capacity of the group to attract and fund PhD students. Similarly, whereas the general funding level appears adequate, most of the grants obtained are modest, precluding the recruitment of post-doctoral fellows, and have to be regularly renewed.

- **Recommandations**

As the team lack full-time scientists, the variety of projects developed may lead to some dispersal, in particular considering topics for which strong international competition exist (e.g. the B regs topic) or for which high technology (involving high costs) may be required (e.g. epigenetics). A prioritization of the topics will be required to allow the team to make important and original scientific contributions.

- **Production results**

The team has an extensive publication record for the 5-year period of 2006-2010 (188 including collaborative works); however, many of these publications are editorials, comments or reviews. Among original research papers in which the team is leader (30 in total), 22 were published in journals with an impact factor >6 (Arthr. Rheum (10), J. Autoimmun (5), J. Immunol (5), FASEB J (1), Cancer Res (1)) and one paper in Blood (IF 10.5). A trend for a progressive increase in the impact factor of the publications can be noted over the last 5 years.

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	8
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	3
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	8/8
A4: Number of HDR granted during the past 4 years	4
A5: Number of PhD granted during the past 4 years	7

3 • Specific comments

- **Appreciation on the results**

The team has a regular scientific output, published in good journals of general immunology (JI) or more specialized in auto-immunity (Arth. Rheum, J. Autoimmun). As a result, the team is internationally recognized in the field of clinical immunology. Among their contributions are studies establishing the importance of the B cell compartment in Sjögren' syndrome, including in the production of the BAFF B-cell survival factor; other contributions concern the editing process in peripheral lymphoid organs, its association with CD5 expression, and its abnormal persistence in auto-immune diseases (Lupus or RA). Finally, a large part of the scientific activity is devoted to the evaluation of therapeutic strategies (Rituximab, IVIg), with an original observation of a direct, non FcgRIIB-mediated, impact of IVIg on B cell signalization through the CD22 receptor. Finally, the team also has a very important clinical activity, being involved in clinical trials, including the coordination of the TEARS cohort, aimed at evaluating the efficacy of Rituximab treatment in Sjögren syndrome performed in 13 different centers.

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

The team has a major regional role in the mentoring of PhD students and appears able to attract, not only students from Brittany universities, but also from abroad (Turkey, Tunisia, Columbia, India), a possibility generated by its strong implication and recognition in international networks in the auto-immune field. The quality of mentoring is attested by awards attributed to PhDs. The team has also developed very good interactions with regional industrial partners, allowing them to collect resources from the professional tax.

This excellent visibility in the auto-immune field, together with this strong industrial partnership with local industries, allowed the organization in 2009 in Brest of the 10th International Symposium on Sjögren' syndrome (the previous one took place in Washington DC and the next one will be in Athens). If this international visibility in the field of auto-immunity is attested by the numerous invitations to international conferences, one should however mention that most of them concerned the previous head of the lab.

A major step forward in the scientific development of the team would be the possibility to recruit post-doctoral scientists, a strategy so far prevented by the lack of adequate funding support. Such a development would be required to achieve the recognition by French research agencies hoped for by the group.

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

Within the specific structure of this team that includes mainly permanent scientists with major teaching and/or clinical duties and PhD students in charge of the realization of the projects, a specific attention is brought to regular and well-structured scientific animation and tutoring, including various types of meetings and exchanges implying also, for some of them, the clinical departments.

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

Several projects have been exposed during the visit, many in the continuity of previous works from the team. The study of a new variant of the BAFF survival factor appears very original and could be of wide relevance; this study is also developed in collaboration with a leading Australian scientist in the field. A very ambitious approach is also engaged in the study of CD5 expression, aiming at characterizing the function of demethylation (and more globally "epigenetics") as a potential deregulation target in auto-immunity. The impact of the B cell compartment in auto-immune diseases will be addressed through their effector function - a new and fast expanding domain-, and more specifically of their possible regulatory role. Immunotherapy by new anti-CD20 antibodies will be studied according to a new angle (the membrane environment of the CD20 molecule), and for IVIg, the role of additional targets at the B-cell surface will be addressed.

The recruitment of a PU-PH with an established expertise in the field of renal transplantation will allow the team to apply its expertise in a new topic, i.e. the role of B cells in the pathogenesis of chronic graft rejection. Valorization through the development of bi-functional antibodies will also be pursued.

The development of animal models is also planned, including a human CD20 transgenic mouse model that will allow the development of graft versus host disease.

In spite of the general focus on B cells common to all these questions, which is the hallmark of this group, the committee felt that the large number of approaches developed would require to be strictly prioritized, in order to mobilize efficiently the resources of the team to the most promising projects.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
IMMUNOLOGIE ET PATHOLOGIE	B	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**

L'Université est une chance

Brest, le 06 avril 2011

Cabinet
Cab n°: 2011/ 146

Affaire suivie par
Pascal GENTE
Vice-Président chargé de la Recherche

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Monsieur,

Je vous prie de bien vouloir trouver ci-joint les observations concernant le rapport d'évaluation Immunologie et Pathologie – 0290346U – **S2UR120001304**.

Vous remerciant de votre diligence,

Je vous prie d'agréer, Monsieur le Directeur, l'expression de mes salutations les plus cordiales.

Le Président de l'Université
de Bretagne Occidentale,

Pour le Président de l'Université
Le 1er Vice-président
Pascal OLIVARD

Georges TYMEN

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Previous director: Pierre Youinou
Future director: Jacques-Olivier Pers

Brest, April 11, 2011
For the attention of the "AERES" experts

Comments on report : S2UR120001304 - Immunologie et Pathologie - 0290346U

We thank the experts for their thoughtful suggestions. We are pleased that they liked our proposal, so that their report is encouraging. This combines a view of the current situation and a summary of the future challenges. Our response is thus restricted to comment some of their recommendations.

1- Quite rightly, their analysis points out that the succession of the former director has long and carefully been prepared. That is, the new director knows the challenges he has to face, and the responsibilities he has to take on, *viz* scientific recognition but also the strong links of the lab with the clinical departments, and the inclusion within an international network.

2- As kindly deplored by the experts, the lack of full-time researchers is a catch-22 problem. Such a scientist is recruited by a team, provided it has been acknowledged by the INSERM, and the other way round, the group is acknowledged, provided it includes full-time researchers. Ours is composed of members with clinical and/or teaching duties. As a matter of fact, the situation would be (will be?) greatly improved following recognition of the team by French research agencies. This constitutes our major objective over the forthcoming contract. With this in mind, two post-doc researchers will be recruited in September 2011.

3- To prioritize research projects in order to effectively assign the bulk of our resources to the most promising projects has already been initiated. For example, studies on anti-endothelial cell antibody and GvH have been given up, to strengthen our visibility in the autoimmune field. This is now restricted to competitive topics, such as “B regs, BAFF and CD5”.

In conclusion, we are fully aware that our forthcoming task is to take these challenges. Needless to say that the experts' advices will be followed to the letter.

Pierre Youinou

Jacques-Olivier Pers

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