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

Section des Unités de recherche

AERES report on the research unit

Laboratory of Immunogenetics of Rheumatoid Arthritis

From the

Université de la Méditerranée

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: Laboratory of Immunogenetics of Rheumatoid Arthritis

Requested label : UMR_S INSERM

N° in the case of renewal: 639

Name of the director: M. Jean ROUDIER

Members of the review committee

Committee chairman

M. Jean-Louis PASQUALI, University Strasbourg, France

Other committee members

Ms Florence APPARAILLY, Université Montpellier, France

Ms Natacha BESSIS, Université Paris 13, France

M. William OLLIER, University of Manchester, UK

M. Lionel PRIN, Université Lille 2, France

Ms Sylvie BABAJKO, Université Denis Diderot Paris 7, France, CSS INSERM representative

Observers

AERES scientific advisor

M. David DOMBROWICZ

University, School and Research Organization representatives

Ms Marie Josèphe LEROY-ZAMIA, INSERM

M. Jean-Louis MEIGE, Université de la Méditerranée

Le membre du CNU n'a pas pu se déplacer.

Report

1 • Introduction

- **Date and execution of the visit**

The visit was organized on February 15, 2011. The visit started at 9:30 and closed at 16:30 with 1 hour break. From 9:40 to 10:00: J ROUDIER (overview program), from 10:00 to 10:30 N. Balandraud who is in charge of the interface between the clinic and the research team, from10:45 to 11:30 I. AUGER on new autoantibodies in RA, and from 11:45 to 12:30 N LAMBERT on microchimerism in RA and systemic sclerosis.

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

This Unit was created in 2004 and was initially located at the Faculty of Medicine La Timone, it was subsequently relocated at Marseille Luminy campus in new Inserm facilities in July 2007. The Unit is now close to the Rheumatology clinical department at Hôpital Ste Marguerite. The Unit is dedicated to understanding the mechanisms involved in the triggering of rheumatoid arthritis and scleroderma, and more precisely the links between HLA DR molecules, disease specific autoantibody responses, and microchimerism.

- **Management team**

The director is M. Jean ROUDIER and the two project leaders are Ms Isabelle AUGER and Mrs Nathalie LAMBERT.

- **Staff members**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	3
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	4
N7: Number of staff members with a HDR or a similar grade	3	4

2 • Overall appreciation on the research unit

- **Summary**

The Unit activity can be described as follows:

- A huge clinical and research effort to produce an internationally recognized database of more than 1000 RA patients who are well phenotyped and HLA typed. It allows the development of novel risk factor table for RA to make more accurate estimates of disease risk and to subdivide the phenotypes of RA patients.

- An innovative strategy has been developed to find new autoantibodies with new diagnostic and/or prognostic values in RA patients. This plan appeared to be initially risky and in a highly competitive field. This translational activity can now be considered to be highly successful.

- An original project on microchimerism in both RA and scleroderma. It builds on the expertise of the team working on microchimerism and HLA. It has already made an important discovery: microchimerism extends the HLA "genetic background" of RA, as susceptibility alleles are present on these acquired microchimeric cells in the patients.

- **Strengths and opportunities**

- Highly creative and innovative team, entirely focused on human auto-immune pathologies;

- Multidisciplinary approach linking clinicians, scientists and now peptide biochemists to capitalize on the patent depositions and the patient database. Typical translational research;

- Intellectual protection of the discoveries: 5 international patents during the last 2 years, 2 others in the pipe line;

- Basic science represents an important research component: identification of new antigens during RA and scleroderma has led and is leading to original hypothesis on mechanisms of diseases, tests of hypothesis, and disease stratification. Importance of microchimerism during RA and scleroderma is also generating new hypotheses that can now be explored;

- Publications in the Top journals in their field (at least 1 or 2 per year);

- Support from the University: during the committee meeting, the president of the scientific council of the University announced 1 future position (MCU-PH), and 1 future technician position that will join the Unit.

- The recent relocation of the clinical department close to the research department facilitates closer working organizations.

- **Weaknesses and threats**

- International collaborations on the first project would further enhance the scope and ambition of the project;

- No postdoctoral fellow;

- No recent publication in a general high Impact Factor journal, with the exception of 1 coauthor publication in the New England Journal of Medicine, and 1 coauthor publication in the Proc. Natl. Acad. Sci. USA;

- Relatively small size of the unit.

- **Recommendations**

- The creativity and productivity of this small unit is indisputable. The projects are well conducted. For example, at this stage of their project and considering the patent depositions, the recruitment of a peptide biochemist perfectly fits with their objectives.

- The publications of the team appear in the top journals of the field (IF >8), but the authors should be more ambitious and submit some of them to higher ranked general journals due to their importance.

- The committee recommends the unit should try to extend international collaborations on clinical sample and data bases relating to early RA, and other national or international collaborations to speed up the biological significance of their discoveries.

- **Production results**

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	1
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	2
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	1
A4: Number of HDR granted during the past 4 years	2
A5: Number of PhD granted during the past 4 years	2

3 • Specific comments

- **Appreciation on the results**

RA does not have a clear animal model, making human research an absolute necessity. InRA patients without anti-cyclic citrullinated peptide (CCP) antibodies, looking for new diagnostic markers, as well as novel biomarkers identifying early arthritis, is highly relevant and appropriate. The team strategy has already been successful and has led to 5 international patent applications. Two novel self antigens have now been published by the team: 1/ the identification of PAD4 (one of the enzymes responsible for protein citrullination and expressed in the joints) as an autoantigen during RA could be an important and fascinating step in the understanding of the presence of many autoantibodies directed against citrullinated proteins during RA; 2/ antibodies against BRAF (a serine threonine kinase) are present in 50% of anti-CCP negative patients and could constitute a new diagnostic tool during the seronegative window of undifferentiated early RA. These results are likely to have an important impact in the field of Rheumatology by permitting early diagnosis of RA and the early treatment required to avoid joint destruction.

The project on microchimerism in RA is also original: the data suggest that microchimeric cells could enhance the genetic background of RA because susceptibility alleles can be present on these acquired microchimeric cells. This description led to an editorial (cover article) in the same issue of Arthritis and Rheumatism journal. This team has contributed significantly to international knowledge illustrated by the frequent and systematic citations in the reviews on microchimerism. The field is fascinating and this team has the capacity to explore the phenomenon identified both in physiology and pathology (expertise for HLA domain, and for microchimerism).

The team, as the project leader (first and/or last author), published 16 peer reviewed papers (Index >4, with 7 papers with Index >7) since December 2005, and 3 editorials. Their best publications (first or last author) are in Arthritis and Rheumatism 2010, 2009, 2007, 2007, 2005, and in Annals of the Rheumatic diseases 2009, 2007. Their research activity led to the deposition of 5 international patents (2 of these, WO2009138408, and WO2010115745, are being considered for license by BIORAD) and 2 new declarations of invention.

The first project is almost monocentric (collaboration with Besançon), but has led to the construction of a high quality and internationally recognized database (1000 RA patients). The project on microchimerism during scleroderma is

based on established international network collaborations (Seattle, Dusseldorf, Bilkent, Bruxelles). These collaborations are still ongoing and already led to 5 publications, 3 of them in journals with IF>8.

Funding: Inserm ProA special program grants (2006 on molecular basis for anti citrullin immunization, and 2007 on microchimerism and autoimmunity); PHRC 2003-2007 on EBV load in RA; Arthritis foundation 2006, 2007, 2009 on New autoantibodies in RA ; GFRS/ASF (groupement français de recherche sur la sclérodermie): 2008 and 2010.

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

The impact of the research is high for clinical translation and medical practice. The director is part of the scientific international board of the European Workshops for Rheumatology Research, he organizes yearly meetings of Southern France Rheumatology research units. He chaired the session on T cell biology at the American college of Rheumatology meeting (2008). The Unit attracted 2 foreign PhD students who are financed by their own countries, although there is no post doctoral fellow.

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

The Unit is relatively small, but functions efficiently without apparent problem (after separate interviews of researchers, technician and administrative, students in the absence of the director) and good atmosphere.

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

The projects are maturing into excellent research themes and, they are innovative. The first project will now develop new diagnostic kits with the help of a new senior scientist in the Unit (peptide biochemist) and they will try to understand the origin and the significance of the 2 new autoantibodies during early RA (mechanistic biological approaches), and will extend the risk factor table for RA with the new data generated in order to further stratify and define subtypes of RA. The second project on microchimerism will describe the physiology of this phenomenon in humans during and after pregnancy, the phenotype of the microchimeric cells, and the possible role of the vanished twin in male microchimerism. Considering the results that have already been obtained, the strategy is valid and highly innovative, and should give new and significant information. The only possible brake could come from the small size of the unit, but as they were presented to the committee, the projects are compatible and achievable with the Unit size.

First project (Autoantibodies): The present table risk factor on 1000 RA patients based on clinical phenotype, detailed HLA types and autoantibodies can now be extended to make the risk evaluation more accurate with the help of clinicians and by the recent recruitment of an Inserm staff computer engineer. The table will be further developed with the addition of new patients and controls, and also with the newly identified autoantibodies. This could give help to delineate novel RA subtypes. The arrival of peptide Biochemists in the Unit is of importance at this stage of the project and they will participate in the optimization of new diagnostic kits. In parallel, the team will investigate some biological aspects of the 2 first target antigens that they described, PAD4 and BRAF. PAD4 is extremely intriguing since it came out from a hypothesis-free driven screening process using high density protein chips, and it precisely the joint expressed enzyme responsible for the citrullination of many proteins (60% of RA patients have anti citrullinated protein antibodies). The team will investigate the possible presence of PAD4 specific T cells in RA patients, according to an original hypothesis they have devised. In summary, the project is innovative, already productive in terms of publications and patents, and will be speeded up with the arrival of biochemists to design appropriate peptides.

Second Project (Microchimerism): The project takes advantage of the known expertise of the team working on HLA diversity, and the expertise on the microchimerism phenomenon. Technical tools were developed to capture the microchimeric cells in order to define their cellular origin in males and females. The tools will be used to define the physiology of microchimerism during normal pregnancy in order to compare the data with patients with RA and scleroderma, the 2 main diseases where microchimerism is thought to play a role. The team will also explore the possible role of a “vanished twin” as a source of microchimerism in male patients with RA and scleroderma. In summary, this project is highly original and innovative and should produce important results in the field.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
IMMUNOGÉNÉTIQUE DE LA POLYARTHRITE RHUMATOÏDE	**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 DE LA MÉDITERRANÉE
AIX-MARSEILLE II

Objet : Réponse au rapport d'évaluation - **S2UR120001640 - Immunogénétique de la polyarthrite rhumatoïde - 0131843H** - de l'unité Immunogénétique de la polyarthrite rhumatoïde

Observations d'Aix-Marseille Université

Aucune observation n'est formulée

En accord avec les deux autres établissements d'Aix-Marseille

Le Président
de l'Université de la Méditerranée

Yvon BERLAND

Le Vice-président du Conseil Scientifique
de l'Université de la Méditerranée

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