IRM - Immuno-rhumatologie moléculaire

Rapport Hcéres

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

Research Units Department

AERES report on unit:

Molecular Immuno-Rheumatology

Under the supervision of the following institutions and research bodies:

University of Strasbourg

INSERM

January 2012

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

Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head

Pierre Glaudes

Unit

Name of unit:	Molecular Immuno-Rheumatology
Acronym of unit:	
Label requested:	UMR-S
Present no.:	EA 4438 (partim)
Name of Director (2009-2012):	Mr Bertrand LUDES
Name of project leader (2013-2017):	Mr Siamak BAHRAM

Members of the committee of experts

Chair:	Mr Dominique CHARRON, Paris
Experts:	Ms Lena ALEXOPOULOU, Marseille
	Mr Joerg H DISTLER, Erlangen, Germany
	Mr Christian JOERGENSEN, Montpellier (representative of INSERM)
	Mr Srini KAVERI, Paris
	Mr David SAADOUN, Paris
	Mr Joerg SCHLAAK, Düsseldorf, Germany
	Mr Antoine TOUBERT, Paris (representative of CNU)
	Mr Richard O WILLIAMS, London, UK

Representatives present during the visit

Scientific Delegate representing AERES:

Mr David DOMBROWICZ

Representative(s) of the unit's supervising institutions and bodies:

Ms Marie-Josèphe LEROY-ZAMIA, INSERM

Mr Eric WESTHOF, University of Strasbourg

Report

1 • Introduction

Date and conduct of visit:

The visit took place as planned at forum Faculté de Médecine on Feb. 25th 2012 from 8 am to 4 pm.

The introduction and overall presentation were made by the project leader Mr Siamak BAHRAM. The scientific presentations were made by Mr Siamak BAHRAM and two other senior scientists. All the participants to the project attended the presentation. A display of posters was set in the hall.

The representatives of the governing institutions, Inserm and University of Strasbourg, were able to confirm and detail their support to the project to the visiting committee.

History and geographical location of the unit, and overall description of its field and activities:

The project proposes the merger of two independent groups on Immunogenetics and Immuno-Rhumatology and located in different buildings. The work force will be unified in one location by the end of 2012.

The title of the application for the unit "molecular immunorhumatology (IRM)" identifies the orevall thematic content of the proposal : The project concerns the "functionnal genomics of auto-immune and auto-inflammatory diseases : "from bench to bedside".

The proposed research is structured in two scientific themes :

- Theme 1: non conventional MHC – I genetics.
- Theme 2: Epigenetics regulation of inflammation

Under these broad objectives, the applicants address two major sets of issues : what is the mode of functioning of certain non-conventional MHC-I molecules MIC genes specially in tissue graft ; MR1 in mucosal immune response and ZAG in immune-linked cachexia. The second issue concerns models pertinent to inflammatory and infectious diseases, specifically rheumatoid arthritis and acute herpesvirus infections. The structure is complemented by a multi-technology plateform.

The translational dimension of the project is highlighted by the "Associated clinicians" in the field of Rhumatology, Transplantation, Nephrology, Allergology Dermatology and Hematology. In close collaboration with these clinics the applicants aim to study the genetics/genomics of auto-immune and auto-inflammatory diseases with the help of the Biomax genomics platform they have established.

Management team:

The merger of the 2 teams is the result of several years of personnal and scientific interactions, and the single location will contribute to the efficiency of the proposed structure. The leadership of Mr Siamak BAHRAM was fully aknowledged by all the team members.

Unit workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	8	7	5
N2: EPST or EPIC researchers	-	-	-
N3: Other professors and researchers	1	1	-
N4: Engineers, technicians and administrative staff *on a permanent position	7	7	
N5: Engineers, technicians and administrative staff * on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	1		
N7: Doctoral students	5		
N8: PhD defended	2		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	5	5	
TOTAL N1 to N7	**23**	**15**	**5**

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the [01/01/2007-06/30/2011] period who will be present in 2013-2017.
Definition and downloading of criteria:
http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

2 • Assessment of the unit

Overall opinion on the unit:

The molecular Immuno-Rheumatology unit is composed of a large group of university scientists, clinicians and engineers that propose a well defined research program of medical importance.

The applicant director has contributed significantly to the field of genetics of non conventional MHC Class I genes particularly by discovering the MIC-A genes and the heads of the merging group have made important observations in the field of auto-Immunity and Rheumatology.

The track record of publication is very good with co-authorship in outstanding publications.

The proposed research objectives of the unit are aimed at further clarifying the physiopathological role of important non-conventional MHC I molecules and at understanding the intricate interactions among genetic, environmental and epigenetic factors (miRNAs) that govern the prevalence of autoimmune diseases such as rheumatoïd arthritis and of infectious diseases such as herpesvirus infection.

The technology genomics and cytomics platform with excellent equipment and specialized workforce is an assurance of the full feasability of the project.

Strengths and opportunities:

The committee underlines the originality and the creativity of the project, and the soundness of the concepts.

The unit performs very good track records and fruitful cooperations .

The close connection between the clinic and the laboratories will ensure an optimal sample collection for translational studies. There is a strong valorisation potential for diagnostic tools and potentially for therapeutics. The experimental data presented are convincing and innovative.

The committee notices the high level of technical competence and the state of the art platform organization in genomics.

The unit receives recognized notoriety and leadership.

Weaknesses and risks:

Some aspects of theme 1 may lead to paths that diverge from the core theme of immuno-rhumatology.

Limited number of full time researchers and post doctoral fellow may be suboptimal for the supervision of an increased number of students in the future.

Recommendations:

The unit should:

- Increase the interconnections between theme 1 and 2;
- Streamline theme 1 by concentrating on MICA/B and theme 2 on rheumatic diseases and auto-immunity;
- Develop a strategy to recruit permanent researchers and post-doctoral fellows.

3 • Detailed assessments

Assessment of scientific quality and production:

The two themes of the proposed unit are original and relevant. The work on the genetics of non conventional MHC Class I molecules is well recognized.

The proposed studies presented by the unit's head on non-conventionnal MHC class I genes are of high calibre and are likely to lead to significant improvements in transplantation medicine. The group has identified molecules that undoubtedly contribute to allograft rejection. The steps to carry this research forward to the clinic, as outlined in the proposal, are well-planned and not over-ambitious. The studies on NKG2DL and MR1 expresion, in tumour immunology and infection, respectively, are also very valuable. Studies on the association between ZAG and immunity and/or inflammation may be seen as a departure from the main programme of work. However, the possible involvement of ZAG in RA-associated cachexia may be worth investigating, given the rheumatological focus of the unit.

The second theme concerning the epigenetic influence on inflammation and autoimmunity particularly in rheumatoïd arthritis and in herpes virus infection is innovative, based on sound concepts. One of the principal investigators and his group have worked on the role of miRNAs in innate antiviral immunity using mice with a mutant DICER gene leading to reduced miRNA expression. Their results suggested that expression of 40 % of miRNAs was reduced in these animals. Such a decrease was also associated with increased expression of IRF7 and a subset of ISGs. They have also demonstrated an increased susceptibility of these mutant mice to MCMV infection which was associated with suppressed IFN production and IRF7 expression.

Leaders of the merging group have worked on the pathophysiology of rheumatoïd arthritis (RA). Their data suggest that MyD88 and FAK are linked and that this crosstalk is involved in the inflammatory response of synoviocytes (FLS). They have also investigated the role of several miRNAs in this disease including miRNA-19, -20 and -346. Futhermore, they have studied the regulation of BAFF synthesis by FLS by TLR ligands and microparticles as well as the role of BAFF in systemic sclerosis.

The research carried out by the proposed unit is original.

Overall, the track record of the scientists is very good. The proposed director is the discoverer of MIC genes and he has published papers in top level journals (see below). Other principal investigators are also prolific producers with a large number of publications in their speciality (see below).

In the past 4 years the team has published 18 basic research papers in peer-review journal, among which 11 as first and/or last author. Most significant papers were published in blood (2011), Mol Immunol (2011, 2008), Plos ONE (2009, 2008, 2007), FEBS (2007) and Virology (2007). Two team members have also contributed to publications in high impact factor journals : Nat Med, 2010, Immunity, 2007 ; PNAS , 2010.

Assessment of the unit's integration into its environment:

The group of associated clinicians is impressive and several PHRC (funding for clinical research) have been obtained reflecting an efficient level of translational medical research.

Valorisation of research is developped via a spin-off of the laboratory as well as through a RD centered Biobank labelised by the Alsace Biovalley Biocluster.

The funding of the group has been successful with peer reviewed grants from ANR, ANRS, ARC. An application for a Labex has been filed by the proposed director.

Assessment of the research unit's reputation and drawing power:

The unit has strong international (Japan, Germany), national (Nantes, Paris) and local cooperations, some of them for a long time. The collaboration with a japanese laboratory is emblematic.

One of the principal investigators is involved in a specialized European Network for miRNAs.

The proposed director was the recipient of the Robert Debré prize for medical research in 2010. He, and a principal investigator, has been invited to lecture at a large number of international conferences. Another team member has recieved the Sirius Prize in 2009.

The capacity to recruit researchers and post doctorants may appear limited perhaps in part due to the highly competitive environnement in Strasbourg.

Assessment of the unit's governance and life:

The organization of the proposed unit is convincing with a clear and accepted leadership and a good communication flow which will be reinforced when the unit will be located in a single site. Unit members demonstrated a strong will and interest for a close cooperation. The interaction with the group of associated clinicians is effective and well organised.

The unit members are fully involved in education particularly in a master program they have developped.

The numbers of senior members, particularly PU-PH, MCU-PH and senior Engineers is adequate to ensure the formation of the young students and scientists.

The core faciliies of the genomics and cytomics platform will contribute to feasibility of the proposed programs.

The implication of the unit and its members at the regional level was evidenced by the discussion with the University of Strasbourg and Inserm regional representative.

Assessment of the strategy and 5-year project:

The unit proposes innovative projects with some of the objectives that have medium- and long-term goals. The applicants have the expertise and equipment to complete the proposed experiments.

Both the themes of the unit have strong clinical interface for studies on transplantation, tumors, autoimmunity and infectious diseases, with long-term projets. The unit ensures adequate funding to run these ambitious projects.

The project on MR1 depends on the successful generation of antibodies. Given that the generation of antibodies is challenging and always unpredictable, this project is to some degree at risk. The tasks involving the conception of pharmacologically-relevant antagomirs to manipulate miRNAs are highly original and to some extent risk-taking. While the focus on epigenetic regulation is novel it will face heavy competition.

The lack of fulltime senior researchers and post-doctorants is a potential limitation.

Overall the strategy for the next five years is well thought and contains a balance of achievable versus higher risk goals.

Assessment of the unit's involvement in training:

The unit has excellent record for teaching and research training activities.

The proposed director is the founder and co-director of a highly successful Master's program "molecular and cellular physiopathology" which has attracted a large number of students to join Master's (M1 and M2) and then on towards Doctoral studies.

Two principal investigators are professors of Rheumatology, two team members are Assistant professors involved in teaching Immunology at the medical school.

All the senior members also occupy teaching positions at the University that allow a direct contact with the formation of the students, and the staff members are also highly implicated in the research internship and training.

Together, the senior members have guided 30 M1 and more than 10 M2 students during the last four years and during this period, they have also supervised 11 PhD students.

The technicians, the students and the senior researchers are satisfied with their work and the conditions within the unit. Despite a lack of postdoctoral fellows, proper supervision is ensured.

4 • Grading

Once the visits for the 2011-2012 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).

This score (A+, A, B, C) concerned each of the four criteria defined by the AERES and was given along with an overall assessment.

With respect to this score, the research unit concerned by this report (and, when necessary, its in-house teams) received the overall assessment and the following grades:

❖ Overall assessment of the unit :

Molecular Immuno-Rheumatology

Unité dont la production et le projet sont très bons. Le rayonnement, l'organisation et l'animation sont excellents.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A	A+	A+	A

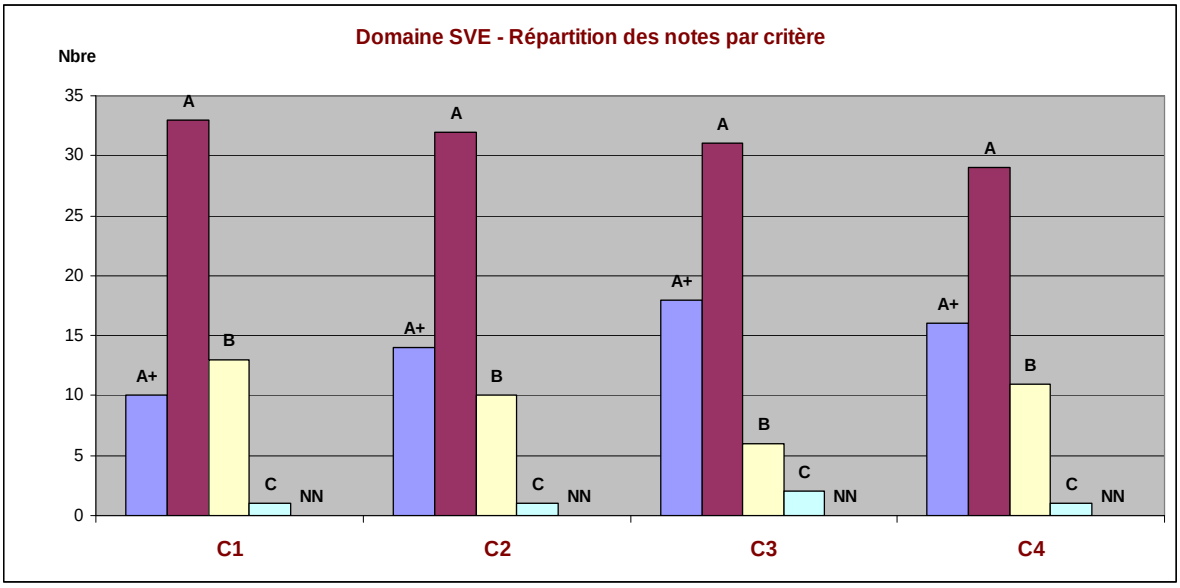
5 ● Statistics per field : SVE au 10/05/2012

Notes

Critères	C2	C2	C3	C4
	Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A+	10	14	18	16
A	33	32	31	29
B	13	10	6	11
C	1	1	2	1
Non noté	-	-	-	-

Pourcentages

Critères	C1	C2	C3	C4
	Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A+	18%	25%	32%	28%
A	58%	56%	54%	51%
B	23%	18%	11%	19%
C	2%	2%	4%	2%
Non noté	-	-	-	-



6 • Supervising bodies' general comments

UNIVERSITÉ DE STRASBOURG

Monsieur Pierre GLORIEUX
Directeur de la Section des Unités de recherche
Agence d'évaluation de la recherche et de l'enseignement supérieur (AERES)
20 rue Vivienne
75002 PARIS

Alain BERETZ
Président

Strasbourg, le 14 mars 2012

Objet : Rapport d'évaluation du projet d'EA Immuno-rhumatologie moléculaire (réf. S2PUR130004558RT)
Réf. : AB/EW/N° 2012-120

Affaire suivie par
Eric WESTHOF
Vice-président Recherche
et formation doctorale
Tél : +33 (0)3 68 85 15 80
eric.westhof@unistra.fr

Direction de la recherche

Cher collègue,

Je vous remercie pour l'évaluation du projet d'équipe d'accueil « Immuno-rhumatologie moléculaire » porté par Monsieur Seiamak Bahram.

Vous trouverez ci-joint les réponses du porteur du projet concernant les erreurs factuelles et les remarques et appréciations du comité d'experts.

Je n'ai pas de remarque particulière à ajouter au nom de l'Université.

Je vous prie d'agréer, Cher Collègue, l'expression de mes sentiments distingués.

Alain BERETZ

4 rue Blaise Pascal
CS 90032
F-67081 STRASBOURG cedex
Tél. : +33 (0)3 68 85 15 80
Fax : +33 (0)3 68 85 12 62
www.unistra.fr

P.J. :

- **Une première partie corrigeant les erreurs factuelles**
- **Une seconde partie comprenant les observations de portée générale**

UNIVERSITÉ DE STRASBOURG

Centre de Recherche d'Immunologie et d'Hématologie

Laboratoire Central d'Immunologie Nouvel Hôpital Civil

Les Hôpitaux Universitaires de STRASBOURG

IMMUNOGENETIQUE MOLECULAIRE HUMAINE

March 13, 2012

Attention:
Agence d'évaluation de la recherche et de l'enseignement supérieur (AERES).

Dear Sir,

We would like to thank the members of the evaluation committee for their effort in analyzing our research output and our future project.

Needless to say that we are extremely happy with this very positive evaluation and do agree with comments that the committee has made to further strengthen the scientific cohesion and the critical mass of our recently unified research endeavor.

May I take this opportunity to inform the AERES that since this evaluation was carried out end of January 2012; the project that I had deposited at the "Investissements d'avenir" has been selected as a **"Laboratory of Excellence" (LabEx)**.

Sincerely yours,

Seiamak BAHRAM

e-signature

Seiamak BAHRAM
Professor of Medicine (PUPH); Immunology.
Director
Immuno-Rhumatologie Moléculaire (IRM)

+33 (0) 3.68.85.39.92
siamak@unistra.fr