Immunogénomique et Inflammation

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Immunogenomics and inflammation

From the

Université de Lyon 1

Mai 2010

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From the

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Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

Mai 2010

Research Unit

Name of the research unit: Immunogenomics and Inflammation

Requested label: Equipe d'accueil

N° in the case of renewal: 4130

Name of the director: M. Pierre MIOSSEC

Members of the review committee

Chairperson

M. Marc BONNEVILLE, Université de Nantes

Other committee members

M. Cem GABAY, Geneva University Hospital, Geneva, Switzerland

M. Frank LUYTEN, Leuven University, Leuven, Belgium

Committee members nominated by staff evaluation committees (CNU, CoNRS, INSERM and INRA CSS....)

M. Pierre YOUINOU, CNU member

Observers

AERES scientific advisor

Ms. Claude-Agnès REYNAUD

University or School representatives

M. Jean-François MORNEX, Université Lyon 1

Report

1 • Introduction

- Date and conduct of the visit:

The site visit started on February 4 at 9:00 AM and ended 1:30 PM. The scientific program included an overall presentation of the team by its director, and 20 - 30 min presentations of the three main topics of the unit, each followed by a 15 - 30 min discussion. After having met staff members (PhD students, laboratory assistants, researchers with permanent position), the Lyon 1 University representative and the Unit director, the committee had a closed-door meeting of 45 min. This thorough presentation adequately complemented the somewhat limited information provided in the written report.

- History and geogrphical location of the unit an brief description of its field of study and activities:

The research unit is located within the Edouard Herriot University Hospital. This unit has been jointly supported by the HCL and BioMérieux since 2002, became an INSERM technological unit (ERT1041) from 2003 to 2006 and an Equipe d'Accueil in 2007. While its main focus is the physiopathological role played by IL-17 in rheumatoid arthritis (RA), the team has been more recently addressing several issues dealing with the effects of IL-17 on cell apoptosis, bone repair, angiogenesis and coagulation.

- Management Team:

The team is headed by a PU-PH (MD-PhD) and develops 3 main research axes dealing with (i) IL-17 pathophysiology and inflammation, (ii) chronicity and repair defect and (iii) response to biotherapy, which involve 2 PhD students, 1 technician and a post-doc (to be hired) for project (i), 1 PH, 1 technician and 1 M2 student for project (ii), and 2 PU-PH, 1 MCU-PH and an ARC (to be hired) for project (iii).

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	3
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)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	4	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	2
N7: Number of staff members with a HDR or a similar grade	3	3

2 • Overall appreciation on the research unit

- Overall opinion

This team has been working for many years on the immunological mechanisms contributing to rheumatoid arthritis (RA), and has made seminal contributions regarding the implication of IL-17 in this process. During the last 5 years, the team has made several original observations regarding the biological properties and possible contribution of IL-17 variants as well as various cellular interplays involving synoviocytes, dendritic cells and T cells to RA pathogenesis. Thanks to solid collaborations with clinicians and industrial partners, the team has also identified several new biomarkers correlating with RA outcome and response to treatments, and keeps on working on the design of new immunotherapeutic approaches targeting the IL-17 inflammatory pathway. The recent scientific output of the team is excellent with numerous papers in the best specialty journals, and the remarkable international visibility of the PI is supported by invited reviews in high profile journals and a recent prestigious award. The project addresses several relevant questions regarding RA pathogenesis, diagnostic and treatment that directly builds on recent achievements of the team. However implementation of some projects regarding vasculogenesis and bone formation and extensions to other chronic inflammatory situations are perceived by the committee as too ambitious for such a small team, and would require strong implication of researchers with specific expertise in molecular biochemistry and/or animal models locally. Moreover in order to secure the future of the team and improve its attractiveness for permanent researchers, the committee recommends the strengthening of its local links with academic laboratories working on related and complementary issues.

- Strengths and opportunities

This team addresses several relevant and original questions with important basic and clinical implications, and strong societal impact.

The scientific output of the team since 2005 has remained excellent, with regular publications in the best specialty journals.

The excellent international visibility of the team director is supported by several invited reviews and international awards.

The team has established an efficient networking with clinicians and industrial partners, which has led to several patents dealing with the identification of several biomarkers with diagnostic and therapeutic interest, and design of promising immunotherapeutic approaches.

The team has obtained several grants from both public agencies and private partners, and secured funding of its research for the coming years.

The team has supervised several PhD students, attracted several foreign postdocs and is currently training several MDs.

Possible integration of the team within several projects involving private companies (eg the Technology Research Institute, with BioMerieux) and academic teams (eg the IHU Transplantation project) represents great opportunities to strengthen its links with local partners.

- Weaknesses and threats

The team has not reached the critical mass that would secure its viability in the long term.

Although it has established efficient interactions with clinical departments locally, the team does not appear to be connected enough with other local research laboratories.

The team has not been able to attract full time researchers, who might be required to develop more mechanistic research.

The project appears too ambitious for such a small team, and the feasibility and competitiveness of some subprojects dealing with angiogenesis and bone formation is not supported by proven expertise in this field.

- Recommendations to the head of the research unit

The team would greatly benefit from recruitment of a high profile and well-positioned researcher. In this regard, it seems that a promising candidate was recently foreseen but has not obtained local support.

The team should focus its efforts on the mechanistic studies dealing with IL-17 and MSC interplay in RA pathogenesis, and clinical studies dealing with characterization of RA biomarkers and immunotherapy.

The team should aim at establishing tighter interactions with other research laboratories with complementary expertise in molecular biochemistry and animal models, in order to secure its long-term viability and enhance its attractiveness for full time researchers.

- Data on the work produced :

(cf. http://www.aeres-evaluation.fr/IMG/pdf/Criteres_Identification_Ensgts-Chercheurs.pdf)

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	1
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	1/1
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	2/3
A4: Number of HDR granted during the past 4 years	0
A5: Number of PhD granted during the past 4 years A6: Any other relevant item in the field	4

3 • Specific comments on the research unit

- Appreciation on the results

Since its seminal observations made more than 10 years ago regarding the role played by IL-17 in RA pathogenesis, the team has studied during the last 5 years (i) the implication of other IL-17 family members in RA, (ii) the subunit composition of IL-17 receptors expressed by various cellular actors contributing to RA (such as synoviocytes), (iii) the cellular interplays involving in particular dendritic cells (DC) and T cells along the inflammatory process, and (iv) the mechanisms underlying synovial hyperplasia and the specific implication of synoviolin, an E3 ubiquitin ligase with antiapoptotic properties, which was shown by the team to be upregulated in patients that do not respond to Infliximab. In parallel the team has assessed the modalities of regulatory T cell induction during chronic inflammation and contribution of mesenchymal stem cells (MSC) and DC to this process. On a diagnostic standpoint, extensive clinical and immunobiological monitoring of RA patients has led to identification of several biomarkers correlating with disease severity or response to treatment. Finally the team has also worked on the optimization of gene transfer approaches into synoviocytes for biotherapeutic purposes, as well as on the fine characterization of newly generated IL-17-blocking mAb. Many of these studies are highly relevant in the field of rheumatology and have significant basic and applied implications. They have led to original observations described in more than 50 publications since 2005, including several papers in the best specialty journals (eg 4 *Rheum Arthritis*, 5 *J Immunol* as leading author) and numerous reviews, some of which in top notch journals such as *N Engl J Med*. Therefore the overall quality of the scientific achievements during the last 5 years is excellent. The team has supervised 6 PhD students since 2005, which is very good output, when considering the rather small size of the team.

- 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 director is highly visible at the international level, as indicated by several invitations to write reviews in prominent journals (in particular in 2009 in the N Engl J Med). Along this line, the PI will receive in 2010 the Carol Nachman Prize, which is a major international award within the rheumatology community. The team has established strong links with several clinical departments working on chronic inflammatory diseases. This has allowed implementation of very good quality translational research supported by competitive national grants (eg PHRC, ANR), with significant implications in the field of biomarkers and immunotherapy. The research training of several M.D. and 4 foreign postdoctoral fellows is also a very positive asset. The team has also long standing interactions with private partners: in particular BioMerieux, which has supported the group since 2002, TcLand as well as Dendritics, a biotech company developing new blocking anti-IL-17 mAbs. Moreover the team director and the PH have issued altogether 4 patents since 2005. The team has established long term collaborations at the national and international level (notably concerning animal models), although it is not involved in any international network supported by public agencies (eg EEC). At the local level, while the team remains a bit isolated within the Rhône-Alpes scientific community, it will nevertheless take part in two projects dealing with the creation of a Technology Research Institute (involving BioMérieux) and an Institut Hospitalo Universitaire on transplantation immunology.

- Appreciation on the strategy, governance and life of the research unit

While the team has managed to run on its own a high quality clinical research, thanks to tight links established with several clinical partners, the lack of strong interactions with other academic laboratories locally has strongly hampered its attractiveness for permanent researchers. Therefore the team has not reached the critical mass required for its long-term stability. In particular there is only one PI (who has additional clinical duties) beside the team director, supervising the work on rheumatology. In this regard, establishment of collaborations with research teams in the vicinity working on more upstream research issues would not only secure the future of the team, but would also strengthen the physiopathological / mechanistic component of the research project (see below).

- Appreciation on the project

The team wishes to address several questions regarding IL-17 immunobiology. In particular a first objective is to assess the biological role of IL-17 and related cytokines (eg IL-17F) on synoviocytes (survival, proliferation and proinflammatory properties), endothelial cells (angiogenesis) and mesenchymal cells (bone formation), and to assess the possible additive or synergistic effect of IL-17 members and other inflammatory factors on the above processes. A second objective is to study into more detail the contribution of synoviolin to inflammation and cell apoptosis, as well as the effect of IL-17 on osteoblastic differentiation through in vitro studies. As a third objective, the team will also pursue clinical studies aiming at (i) identifying new markers of response to treatment based on the IL-17 signature, and (ii) assessing new immunotherapy approaches based on combined blockade of IL-17A and F on the one hand, and triggering of regulatory T cells on the other hand. The project is very ambitious and covers many questions that not only deal with the mechanisms underlying chronic inflammation of rheumatic diseases, but also with the mechanisms of vasculogenesis and osteogenesis. Analysis of the role played by IL-17, synoviolin and MSC interplays in rheumatoid arthritis, and its diagnostic and therapeutic developments, are clearly relevant, build on proven expertise of the team in this area, and will benefit from secured funding and excellent clinical networking. However the projects dealing with vasculogenesis/angiogenesis and bone formation are much more risky and appear too descriptive. In the absence of strong interactions with specialists in the latter two fields who master both in vitro and in vivo models, the team should put most of its efforts on the first and third objectives, and prioritize the work on rheumatoid arthritis rather than diversifying the clinical indications. It will be also important to strengthen in-house expertise in animal models and/or molecular biochemistry approaches, which might be challenging if the team is unable to attract permanent researchers.

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+	B	B

Université Claude Bernard Lyon 1

Le Président
Lionel Collet

Villeurbanne, le 24 Mars 2010

M. 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 de recherche :

«Immunogénomique et inflammation» 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

Lionel Collet