Cellules souches mesenchymateuse et environnement articulaire, immunothérapie de la PR

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Immuno-Rheumatology therapeutical Unit

From the

University of Montpellier 1

INSERM

Mai 2010

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Le Président de l'AERES	Section des unités de recherche
	Le Directeur
Jean-François Dhainaut	Pierre Glorieux

Mai 2010

Research Unit

Name of the research unit: Imuno-Rheumatology therapeutical Unit

Requested label: UMR_ INSERM

N° in the case of renewal

Name of the director: M. Christian JORGENSEN

Members of the review committee

Chairperson

M. Jean ROUDIER, Parc Scientifique de Luminy, Marseille

Other committee members

M. Wim B. Van Den BERG, University of Nijmegen, The Netherlands

M. Dominique BAETEN, University of Amsterdam, The Netherlands

M. Jean-Louis PASQUALI, CNRS, Strasbourg

M. Francesco DAZZI, Imperial College, London, Great-Britain

Mrs Paola MIGLIORINI, University of Pisa, Italy

M. Maxime BREBAN, Institut Cochin, Paris

Committee members nomminated by staff evaluation committees

M. Olivier CHOSIDOW, CNU member

Mrs Sylvie BABAJKO, INSERM CSS member

Observers

AERES scientific advisor

M. Jean Antoine LEPESANT

University representative

M. Jacques MERCIER, Université Montpellier 1

Inserm representative

Mrs Marie Josèphe LEROY-ZAMIA

Report

1 • Introduction

- **Date and execution of the visit:**

The AERES committee visited the U844 unit on the 14th of January, 2010. The visit started at 9 a.m. and ended at 4 p.m. The director first gave a general presentation of the Unit. Then, the 5 project leaders presented their work and research programs. Finally, the director gave an overview of the Unit activity and future projects. In the afternoon, the committee met with permanent research staff, technicians and students, then with University and Inserm representatives. The visit ended with a closed door meeting of the committee members.

- **History and geographical localization of the research unit, and briefpresentation of its field and scientific activities:**

This Unit was created in 2007. It is hosted in the Institute of Neurosciences in Montpellier. Its field of work is bone and joint diseases. Its main projects involve analysis and search for new therapies in rheumatoid arthritis, osteoarthritis and bone metastases.

- **Management team:**

This unit is divided into two teams: the first team is dedicated to rheumatoid arthritis (RA) and directed by 3 co-leaders; the second team is dedicated to mesenchymal stromal cells (MSC) in osteoarthritis and bone metastasis and has two co-leaders.

- **Staff members:**

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	11
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	6
N7: Number of staff members with a HDR or a similar grade	7

2 • Overall appreciation on the research unit

- **Overall opinion:**

The committee members were all impressed by the energy and enthusiasm carried by the group leader and transmitted to the whole unit. This is a recently created unit which is still in a growing phase, with a very good potential for the future. They aim at bringing their innovative and risky work to clinical applications very soon, which is also quite unique. The unit activities can be divided in two themes developed by two teams : (i) rheumatoid arthritis, and (ii) mesenchymal stromal cells in osteoarthritis and bone metastasis.

The rheumatoid arthritis part is very good. The mesenchymal stromal cell part contains an osteoarthritis subpart judged excellent and a bone metastasis part judged good but somewhat out of the main research area of the unit. This will be discussed later but the bottomline is that this laboratory is mostly working in the field of rheumatic diseases and the bone metastasis project is not part of this field.

- **Strenghts and opportunities:**

The director is a very charismatic and enthusiastic unit leader. His orientation of the activities of the unit towards translational research is very good. The laboratory has a high national and internationale visibility with many research grants, a large number of collaborations and a great ambition. The atmosphere in the unit is relaxed, joyful and optimistic and it shows. The unit is attractive as 4 researchers joined the group in the last two years.

- **Weaknesses and threats:**

For all his energy, the director has a tendency to do too many things and consequently to branch out too much. In this respect, the bone metastasis subpart of the mesenchymal stromal cell team does not fit too well with the rest of the activities of the laboratory.

The common denominator for the whole unit remains using stem cells to treat arthritis and osteoarthritis. This in itself is a huge program. It should be restricted to one or two very focused projects in each field.

- **Recommendations to the head of the research unit:**

The committee wishes to encourage the unit to keep as closely focussed as possible on bone diseases and rheumatology. Indeed, the unit is already following two highly competitive pathways: rheumatoid arthritis and osteoarthritis. A third one related to cancer seems too much and leads to dispersion.

- **Production results:**

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	14
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	4
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	100%
A4: Number of HDR granted during the past 4 years	
A5: Number of PhD granted during the past 4 years	4

3 • Specific comments

- **Appreciation on the results:**

This unit develops an original research with strong translational applications. It is one of the international leaders in MSC and RA.

The most important result from this laboratory was the demonstration, that mesenchymal stem cells can be immunosuppressive in animal models of arthritis. This was published in Blood at the end of 2003. From then on, this article oriented the lab's activity, both for the arthritis and the osteoarthritis teams, towards using mesenchymal stem cells for different purposes (immunosuppression and cartilage repair and reconstruction).

The unit managed in a few years to produce a steady and consistent number of publications in top journals in the specific fields of interest (rheumatology, ...) and already achieved to publish a few papers in general journals.

Unit members signed or cosigned 100 publications in the last five years. However, most of them are collaborative or review articles. Original research articles originating from the laboratory number around 20. They were published in Arthritis and Rheumatism (CI=7), Annals of the Rheumatic Diseases (CI=7), Journal of Immunology (7), Transplantation (4), Human Gene Therapy (4), Journal of gene Medicine (3), Bone (4), Stem Cells (7.7).

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

The head of the unit is regularly invited to international conferences (15 invitations in the last 4 years). He and his colleagues organized 4 national and international meetings. Four researchers, 6 phD students and one postdoc joined the unit in the last two years.

This Unit is outstanding in its success in getting its grant applications funded. The head of the unit coordinates an FP7 European program on stromal cells derived from adipose tissue for the treatment of osteoarthritis. Another researcher in the group co-coordinates an FP7 grant on TRAPS. The unit also participates in an FP6 grant on "Curing autoimmune disease". Four ANR contracts have been obtained in the past 4 years. Everything considered, this unit raises 400.000 Euros of its 600.000 Euro annual budget in contract grants.

The head of the unit does an outstanding work through his personality in being involved in international or national scientific networks and establishing stable collaborations with foreign partners. This is best illustrated by his taking part in 3 European programs.

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

The head of the unit is a very good leader who brings enthusiasm to his troops. In general, he goes for many high-risk original projects, with a practical purpose. There is a high-risk translational research carried out in the unit.

The unit is very friendly and cooperative both internally and externally. It is involved in many European Grants. However, this very connective strategy has one drawback: it is somewhat difficult to keep track of the core of the Unit's projects, and of what actually originated from within the Unit.

The Unit members demonstrate a very active initiative in organizing and teaching research.

- **Appreciation on the project:**

The research project, comprising an arthritis therapy part and a mesenchymal stromal cell part is very good and high risk and very translational. However, it may be too widespread and some questions are less relevant. This will be discussed later in the team by team analysis. There is a very good originality and risk-taking.

4 • Appreciation team by team

Team 1: Cell and gene based immunotherapy in arthritis

Team leaders: M. Hans Hissel, Mrs Florence Apparailly and Mrs Pascale Louis-Plence

- **Staff members:**

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	4
N7: Number of staff members with a HDR or a similar grade	4

- **Appreciation on the results:**

The arthritis project includes three parts: (1) Th17 cells in arthritis, influence of miRNAs on their development, elimination by anti CCR6 antibody. (2) miRNAs in chronic inflammatory arthritis, their role and usage in therapy. And (3) Regulatory T cells in the treatment of RA.

The TH17 project is good, the anti CCR6 elimination part is judged acceptable and the miRNAs in TH17 development part is judged very good. The micro RNA in inflammatory arthritis project was judged globally outstanding, new and exciting. The Regulatory T cell project was received with less enthusiasm by the committee, because, although it is good, it is somewhat out of the unit's field.

Ten articles were published on this topic. Half of them were in journals of impact factor between 5 and 10, which is considered as good. Four patents have been applied for since 2005.

One of the strengths of this team is its ability to raise funds and participate in very good and stable collaborative networks with European teams. It is involved in one FP6 program on arthritis and holds a number of public and private contracts.

One international patent is owned together with the Academic medical Center of Amsterdam on vectors for gene therapy in arthritis. Clinical trials with industrial partnership are considered on TR1 treatment of arthritis and antiCCR6 treatment of arthritis.

- **Appreciation on the strategy, governance and life of the team:**

The arthritis team is well organized, coordinated. Its three subteams fit together well. The microRNA project is really fueling this whole team and constitutes its main force. The unit members are heavily involved in teaching and student training.

- **Appreciation on the project:**

This is a long-term project with practical applications in the treatment of arthritis.The microRNA project is particularly original.

- **Conclusion:**

— Overall appreciation:

The arthritis therapy team develops a good research applied to the treatment of inflammatory arthritis. There is a strong adequacy between human resources, funds and research field of this team.

— Strengths and opportunities:

The main strength of this team, besides the enthusiasm and connexion with a very good clinical center involved in the treatment of RA, is the microRNA approach which fuels the Th17 subgroup and the microRNA subgroup.

— Weaknesses and threats:

The weak point of this team may be the Regulatory T cell project. The Th17 team is considered solid, but the microRNA part (in the development of TH17 cells) is seen as more original and more promising than the anti CCR6 part.

— Recommendations:

Keep on doing good work and try really to take advantage of the miRNA technology you have developed.

Team 2 : Stromal cells in osteoarthritis and bone metastasis

Team leaders: Mrs Danièle Noel and Mrs Gwendal Lazennec

- **Staff members:**

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	7
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	2
N7: Number of staff members with a HDR or a similar grade	3

- **Appreciation on the results:**

This team is divided in two subteams. One works on cartilage damage and cartilage development and repair. The other led by Gwendal Lazennec works on stromal cells, chemokines and cancer. The cartilage damage/repair project includes 5 subparts: 1/mi RNA expression in chondrocytes, 2/Chondogenesis inducing scaffolds, 3/Treatment of osteoarthritis with adipose tissue stromal cells, 4/miRNAs in cartilage degenerescence, 5/molecular events in tissue regeneration in the MRL/Mpj mouse. The whole cartilage damage/repair project generated great enthusiasm among committee members, especially the tissue regeneration in MRL/Mpj mouse.

The stromal cells, cytokine and cancer project was evaluated as good. The PI has a good history in cancer biology which has also produced good funding and publications, thus indicating that he is well connected in the field. He has made considerable efforts to join the major theme of the unit by tackling the role of MSC - a joint/bone cell player - in his original field (cancer) and this should be appreciated. Ideally the committee would like to see that he is slowly developing a research programme that will allow him to branch out into the rheumatology theme to which all investigators have committed.

Publication number is on the average 10 per year, half of them in journals whose impact ranges from 5 to 10. This is considered as good by the committee.

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

The team has developed numerous and excellent and stable partnerships. It heads a European FP7 program on the treatment of osteoarthritis with adipose stromal cells (ADIPOA project). The team ahs secured numerous other public and private grants. Concrete results of the research activity and socio-economic partnerships. The team is also very good at performing translational research.

- **Appreciation on the project:**

The whole cartilage project is original, ambitious with a high degree of risk –taking, and practical. It made a great impression on the committee.

- **Conclusion:**

— Overall appreciation:

This team is heterogeneous. Its osteoarthritis/cartilage part is outstanding, very promising. Its cancer part is good but somewhat irrelevant in this unit.

— Strengths and opportunities:

Original, creative, well funded translational research in the vacant field of osteoarthritis treatment.

— Weaknesses and threats:

There is a clear danger of dispersion which should be taken into consideration.

— Recommendations:

This overall excellent research team could get even better if the team which works on bone metastasis could somewhat reorient its activity towards the main force of the laboratory, which is arthritis and osteoarthritis.

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+**	**A+**	**A**

Nom de l'équipe : *CELL AND GENE BASED IMMUNOTHERAPY IN ARTHRITIS*

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	*A*	*A+*	*A+*	*A*

Nom de l'équipe : *STROMAL CELLS IN OSTEOARTHRITIS AND BONE METASTASIS*

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	*A*	*A+*	*A*	*A*

Administration Droit Economie Gestion Médecine Odontologie Pharmacie Sports

Université Montpellier 1

Montpellier, le 15 avril 2010

Le Président
Ph.A/NG
Départ 2010 – 218

Monsieur Pierre GLORIEUX
Directeur de la section des unités
de recherche
Agence d'Evaluation de la Recherche et de
l'Enseignement Supérieur (AERES)
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75002 PARIS

Monsieur le Directeur,

Je vous adresse mes remerciements pour la qualité du rapport d'évaluation fourni à l'issue de la visite du comité d'expertise concernant l'unité de recherche **«Cellules souches mésenchymateuses, environnement articulaire et immunothérapie de la polyarthrite rhumatoïde»**

Vous trouverez ci-joint les réponses du Directeur de l'unité auxquelles le Vice Président du Conseil Scientifique et moi-même n'avons aucune remarque particulière à rajouter.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de ma considération distinguée.

Philippe AUGE

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Unité de Recherche 844

Cellules souches mésenchymateuses, environnement articulaire et immunothérapies de la Polyarthrite Rhumatoïde

Directeur Christian Jorgensen

Montpellier, le 12 avril 2010

Monsieur le Président
Comité de Visite AERES

Nous tenons à remercier l'ensemble des membres du Comité de Visite qui a évalué notre unité INSERM U844.

Le rapport met en évidence les points forts de l'unité dont le dynamisme et la production scientifique avec plus de 30 articles publiés sur les trois dernières années et sept brevets déposés par notre unité. Le comité reconnait l'excellente visibilité à l'échelon européen ce qui lui a permis de participer à 3 projets européens et d'en coordonner ADIPOA dans le cadre du programme FP7. L'unité a pu obtenir des financements par l'ANR et également par le Pôle de Compétitivité dont le projet FIU Cellarthrix, dans ce projet la partie T régulateurs doit rester un axe fort pour notre unité. Le comité met en avant l'innovation et la recherche translationnelle appliquée aux maladies ostéoarticulaires basée tant sur les cellules immunitaires que sur les cellules souches mésenchymateuses. Ceci est rendu possible grâce à un important partenariat clinique avec les départements de rhumatologie et orthopédie du CHU de Montpellier.

Le projet de l'unité est centré sur l'innovation thérapeutique dans les maladies ostéo-articulaires, se basant sur l'immunothérapie ciblant Th17 CCR6, et l'identification des microRNA impliqués dans la réponse autoimmune et l'arthrite rhumatoïde. Dans ces domaines, les projets sont classés par le comité comme de très bons à excellents par le comité. Enfin, nous avons été dans les premiers à montrer l'effet immunosuppresseur des cellules mésenchymateuses et le potentiel thérapeutique de ces cellules appliquées dans les modèles d'arthrite. Le comité évoque la place de l'activité de cancérologie. Il s'agit d'un projet original sur interaction carcinome et MSC dans le processus de métastases osseuses. Dans le cadre de nos thérapies cellulaires, le contrôle du risque oncologique est important, et cette activité doit à notre sens s'intégrer dans cet axe de recherche.
Comme le souligne le comité, l'unité est attractive avec l'accueil de chercheurs étrangers (indien, norvégien, américain et lituanien) et le renforcement de l'équipe par l'arrivée de 4 chercheurs statutaires. Enfin, nous avons recruté un chercheur CR2 en 2009 qui conduit un projet original avec prise de risques mais avec un potentiel d'innovation important.

Pr Christian JORGENSEN

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