UDEAR - Unité de différenciation épidermique et autoimmunité rhumatoïde

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Epidermal differentiation and rheumatoid autoimmunity

From the

University Toulouse 3

CNRS

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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: "Différenciation Epidermique et autoimmunité rhumatoïde"

Requested label: UMR CNRS and UMR_S INSERM

N° in the case of renewal:

Name of the director: M. Guy SERRE

Members of the review committee

Chairperson

M. Jean ROUDIER, Parc Scientifique de Luminy, Marseille

Other committee members

Mrs Inga MELCHERS, University of Freiburg, Germany

M. Jonathan EDWARDS, University College London, United-Kingdom

M. Dirk ELEWAUT, Ghent University, Belgium

Mrs Nicole BASSET-SEGUIN, Hôpital Saint-Louis, Paris

M. Rainer SCHMIDT, Skin Research Consulting, Paris

Mrs Laurence MICHEL, Hôpital Saint-Louis, Paris

Committee members nominated by staff evaluation committees

Mrs Jacqueline CAPEAU, CNU member

M. Ulrich BLANK, CoNRS member

M. Lionel LARUE, INSERM CSS member

Observers

AERES scientific advisor

M. Jean Antoine LEPESANT

University or School representative

M. Hugues CHAP, University Toulouse 3

Research Organization representatives

Mrs Sylviane MULLER, INSB-CNRS representative

Mrs Armelle REGNAULT, INSERM representative

Mrs Armelle BARELLI, Head of Midi-Pyrénées regional, CNRS administration

Mrs Mireille BLANC, Head of Midi-Pyrénées Limousin regional, INSERM administration

Report

1 • Introduction

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

The evaluation committee visited UMR 5165 on December 8, 2009, from 8.30 a.m. to 6 p.m. The visit started with a general presentation of the unit's activity by Guy Serre. Then, scientists from Teams 1, 2 and 3 gave a 45 minutes presentation of the activity of each team. After lunch, members of the committee met with research staff, post docs and students, then with technical staff, and finally with representatives of CNRS, INSERM and Université Paul Sabatier before members of the evaluation committee discussed the visit and the report to be written.

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

This research unit has been working at hopital Purpan, under the same leadership, since 1991. Its two research subjects have been, from the start, the differentiation of keratinocytes and autoantibodies in rheumatoid arthritis (RA). Under its current form, the unit includes 3 teams: Team 1 focuses on keratinocytes, Team 2 on auto-antibodies in RA, Team 3, just arriving, works on animal models, dendrimers and clinical studies in RA.

- **Management team:**

This Unit was previously divided into three groups: 2 were focussing on skin biology and one on rheumatoid arthritis. With this new application, it will be different: one team will continue working on skin (this team is a fusion of the two previous skin biology teams) and the two others will focus on rheumatoid arthritis. The first of the two Rheumatoid arthritis teams is headed by the Unit's Director, Guy Serre. The second rheumatoid arthritis team is just joining the lab. It will be headed by M. Jean-Luc Davignon and focuses on animal models and a new treatment of RA.

- **Staff members:**

	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	9
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)	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	13
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1
N6: Number of Ph.D. students (Form 2.8 of the application file)	7
N7: Number of staff members with a HDR or a similar grade	6

2 • Overall appreciation on the research unit

- **Overall opinion:**

The review panel unanimously agrees on the high present quality and future potential of the research unit, which after important renovation work supported by European Community funds and the CNRS (total investment ~ 1.3 Millions Euros) has been finally regrouped in 2007 in a completely renovated building on the Purpan hospital site in Toulouse. Historically, this Unit has been constructed around two research topics, one centered around keratinocyte biology and epidermal barrier function (Former Teams 1 and 2), the other centered around the diagnosis, pathophysiology and immunotherapy of rheumatoid arthritis (RA) (Former Team 3). Despite these seemingly different subjects, there are multipe interactions, both technological and scientific (citrullinated proteins, peptidylarginine deiminases). During the past years the research teams have produced solid science with significant contributions to their respective speciality. More specifically former team 3 has made an outstanding contribution by describing and characterizing a highly specific new biomarker (autoantibodies to citrullinated fibrin) for RA. Former Teams 1 and 2 have made important contributions in the description and initial characterization of new genes and proteins associated with terminal keratonocyte differentiation and epithelial barrier function. A true strength of the Unit is the director's ability to attract funds from industry, which besides financing fundamental research allows for immediate translation ot their research into industrial applications. This is also supported by the important number of patents filed during the research term. The new restructured project proposed by the director will keep the present research topics centered around dermatology (New Team 1) and RA (New Teams 2 and 3). An important effort will be made to integrate clinical research in view of translating their research into clinical applications. While teams 1 and 2 are globally expected to continue their high level research in their respective fields, team 3 created to reinforce research on experimental models in RA and clinical research applications appears heterogenous and the true independency from team 2 remains to be proven.

- **Strengths and opportunities:**

This is good fundamental research applied to clinical problems in dermatology and rheumatology.

Teams 1 and 2 are already leaders in their fields. The arrival of Team 3 may allow Team 2 a simpler access to animal models and clinical trials in rheumatoid arthritis. Indeed, the leading scientist in team 3 has extensive experience in mouse and rat models of autoimmunity. It could be a major help for team 2.

- **Weaknesses and threats:**

Team 1 presented a research program that seemed too widespread.

Team 3 is not (yet?) at the level of team 2.

The interactions between the different categories of staff personnel could be improved. Indeed, there is some separation between technicians, students and research staff, all located at different places. This does not help communication between different members of the team. Overall, less hierachy would make the Unit a more efficient place.

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

General management: students wish to travel abroad. Technicians would like less hierarchy. They asked to have more interactions with the rest of the scientists. They also asked to be included in the authorship of research articles if their own work deserves it.

Science: The committee recommends that the number of topics studied should be reduced. Indeed, we agree that the dermatology and rheumatology projects are both healthy and successful but it is not clear that the third arthritis project is absolutely necessary.

Team 3 should be given a chance to reach independence in the next 4 years. If it doesn't, it should integrate Team 2.

- **Data on the work produced:**

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	15
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)]	1
A4: Number of HDR granted during the past 4 years	0
A5: Number of PhD granted during the past 4 years	7

3 • Specific comments on the research unit

- **Appreciation on the results:**

Team 1 and Team 2 have produced very high quality research in the last 5 years and are expected to continue. Team 2 has capitalized on its discovery of anticitrullin immunization and has kept analyzing and developing the system. Team 1 has identified genes expressed by granulous keratinocytes, performed in vitro studies of corneodesmosin (another child of this lab) function, and studied the PADI genes, which encode Peptidyl Arginyl Deiminases.

This laboratory publishes in the best journals in its two specialties : Arthritis and Rheumatism, Annals of the Rheumatic Diseases, Journal of Immunology, Journal of Biological Chemistry, Journal of Investigative Dermatology. These articles really originate from the laboratory. Researchers from the unit present papers at international meetings and are often invited as lecturers.

The unit has developed long-lasting partnerships with companies in the fields of cosmetic industry (Chanel, Pierre Fabre) and biodiagnosis (Biomérieux). This allows the hiring of many postdocs and students.

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

Unit members have received more than 20 invitations to present data at international symposia during the last four years period. Most remarkably, a team member was invited to present his data at two Gordon Conferences, in 2007 and 2009. Another one received also multiple international invitations, including one at the Kennedy Institute of Rheumatology. Both the dermatology and the rheumatology teams have many international collaborations.

The number of post-docs is low. The number of foreigners is low.

The head of the lab has been very successful at raising private and public funding, both to fund ongoing research and to pay for the complete rebuild of the current building, for which he obtained European funds from FSE and FEDER.

Major Private donors are: Chanel, Biomérieux, Pierre Fabre, Major Public donors are: ANR, INSERM ProA, ARP-Arthritis Fondation Clarins, Société Française de Dermatologie, Fondation de l'Avenir, Genoscope, Institut des Maladies Rares.

This lab has developed many national and international connections in France, Europe and Japan. Partnerships with industry are remarkable, with a special link with the cosmetics industry (Chanel, Pierre Fabre). Numerous patents have been obtained.

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

External communication has been very good with the organization of international and national symposia, the most famous of which is the 28th European Workshop for Rheumatology Research (EWRR), organized in Toulouse in 2008 (EWRR is the top research workshop in European Rheumatology). Internal communication could be somewhat improved by erasing hierarchical and geographical frontiers between research technicians and researchers.

Team 2 is now the obvious leader of this lab, with an extremely ambitious and creative project towards the treatment of RA by specific immunosuppression to eliminate anti citrullin immunity. This is truly outstanding.

10 to 15 Unit Members actively participate in teaching each year.

- **Appreciation on the project:**

Both the keratinocyte and the arthritis projects have been successfully pursued over many years. There is no doubt they will keep being successful. The Rheumatoid arthritis selective immunosupression project is really clean and creative. Indeed, what is proposed in rheumatoid arthritis is to perform epitope specific immunosuppression. This has not been done in any autoimmune disease yet. This is possible here because this team has defined 2 citrullinated epitopes on fibrin, which are recognized by almost every patient.

4 • Appreciation team by team

Team 1: Keratinocyte differentiation and epidermal barrier

Team leader: M. Michel SIMON

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

	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	6
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0
N6: Number of Ph.D. students (Form 2.8 of the application file)	4
N7: Number of staff members with a HDR or a similar grade	3

- **Appreciation on the results:**

In this team, some members have been involved in the characterization of key molecular elements in skin barrier and hydratation, while others have used transcriptome analysis of granular keratinocytes to identify new potential targets of skin barrier function. Team 1 is the world leader in skin biology for the study of corneodesmosine and the biology of the stratum corneum (from 14 articles, 7 are associated with the leader of team 1 since 1997). Their results have an impact on the molecular understanding of cutaneous diseases with a dysfunction of skin barrier such as psoriasis and atopic dermatitis. Their work should also help to develop new therapeutic strategies in dermatology.

The team has published 25 original papers most of them in high quality journals, either of the speciality or generalist. There have been 86 communications at national or international meetings with 24 invited conferences and seminars, including 2 Gordon Conferences. 8 PhD thesis, one patent, 2 thesis prizes and one prize for the best communication.

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

This team is an international leader in skin barrier function. It has established excellent collaborations with various French laboratories and international groups, in particular with Japanese groups. It has shown a strong ability to raise funds in particular from industry. It has also developed a long lasting collaboration with the local Pierre Fabre group. The participation to international or national scientific networks is extremely good, in particular with Japan.

The team has attracted 4 post docs and 6 students, some of them from foreign countries.

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

The committee has noted interesting parallel approaches, with both complementary and synergy, in both technical and molecular areas between team 1 and team 2: focus on the analysis of the epidermis leads to interactions through PAD and new biotherapies. Students and post-docs seem to be satisfied with the relationship with their team leader.

The team contributes to the unit's facilities, with biochemical and transcriptomic approaches. The team leader demonstrated potent capacities to follow the scientific project and to interact with other teams within the unit and with other external partners in Toulouse (IFR, Pierre Fabre…). The recent collaboration with the Dermatological department provides potent scientific development in the pathophysiology of skin barrier diseases.

There is a strong and regular teaching activity of all members of the team and an involvement in the organization of local and national meetings.

- **Appreciation on the project:**

The project is original and aims at characterizing key events of the skin barrier functions. Numerous applications at the clinical levels should arise in the future. The projects have been going on for many years with a good international input and should continue in the same way.

- **Conclusion and recommendations:**

This is a very original and outstanding project by a team which is a world leader in its field.

- **Strengths and opportunities:**

They lie in the originality of the project and the availability of new tools at hands.

- **Weaknesses and threats:**

The molecular and clinical projects are quite ambitious, especially for the clinical part and should remain more focused.

Team 2: Autoantibodies to citrullinated poteins

Team leader: M. Guy SERRE

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

	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	7
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1
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)	4
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)	3
N7: Number of staff members with a HDR or a similar grade	1

- **Appreciation on the results:**

This team has made a major breakthrough in the understanding of rheumatoid arthritis when it discovered that the so called anti filaggrin and anti keratin autoantibodies, specific for RA, actually recognized citrullin residues on different proteins like Filaggrin and Fibrin. This discovery was the basis for the current diagnosis test: detection of anti citrullinated protein antibodies.

Since then, this team has been an international frontrunner in the field of anti citrullin immunization. This new proposal keeps the same level of scientific sharpness and ambition. Indeed, it now proposes to treat RA by specific suppression of anti citrullinated fibrinogen autoimmunity.

This team has developed a very strong partnership both with private and public sponsors and with collaborating teams in France, Europe and Japan.

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

This is the strongest French team in the field of rheumatology. It has provided a major breakthrough in the understanding of RA with the discovery of anti citrullin immunization. It therefore attracts both funding, collaborations and students. The team leader has been invited 12 times at international meetings in the last 5 years.

This team has been extremely successful in attracting public (INSERM ProA, ANR, Arthritis Fondation) and private (Biomérieux) funding.

The team has strong collaborations in France (Strasbourg, Marseille, Evry), Europe (Holland, Austria) and Japan.

Since 2005, this team has published 14 original articles (4 in "Arthritis and Rheumatism", the best journal in the field of Rheumatology, 2 in "The Annals of the Rheumatic Diseases", the second best, 1 in "The Journal of Immunology", 1 in "The European Journal of Immunology", and finally, 1 in "The Journal of Experimental Medicine"). There were 27 international presentations of which 12 were invited lectures, 2 PhD Theses. Last but not least, 4 patents were delivered to this team (2 international patents in 2005, 1 national in 2007, 1 national in 2009).

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

Governance could be softer with technicians and students who would like to attend international meetings and travel abroad. The unit's members are involved in intensive teaching activities. The team leader is in charge of organizing the whole teaching in Cell Biology in the 2 medical schools in Toulouse.

- **Appreciation on the project:**

The whole project has been at the cutting edge for 15 years. The current project is ambitious, well thought, well organized. It may conduct to a specific treatment of RA by specific depletion of auto-antibodies against citrullinated fibrin or specific elimination of the cells which make them.

- **Conclusion:**

— Overall appreciation :

This project is outstanding. Indeed, it started with the breakthrough discovery of anti citrullin immunization in this Unit. This project moved on in a very linear way. Fibrin was identified as the major citrullinated antigen in the joint. Two dominant epitopes on citrullinated fibrin were identified. One or the other epitope are recognized by most patients. They will be used now for specific tolerization. So this is a very innovative project with everything from basic discovery to pratical application for treatment in a very common autoimmune disease.

— Strengths and opportunities :

Well thought, ambitious, alreday leader in this field. What is outstanding is the linear evolution of the project: discovery of anti citrullin immunization, demonstration that fibrin is the major joint citrullinated antigen, mapping of two dominant epitopes on citrullinated fibrin, tolerization to these two epitopes to cure RA.

— Recommendations :

Keep on doing good work.

Team 3: Experimental pathology and new treatments in RA

Team leader: Jean Luc DAVIGNON

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

	Future
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)	1
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)	3
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)	4
N7: Number of staff members with a HDR or a similar grade	3

- **Appreciation on the results:**

This team will be the result of the merger between the JE2510 (Jeune Equipe 2510) a University research unit created in 2007 (centered around experimental therapeutic approaches of RA) and a researcher from Inserm U563 who has developed phosphorus-based dendrimers with immunomodulatory potential. The goal of this research team is to develop animal models of rheumatoid arthritis in order to define in close collaboration with team 2 major pathophysiologic components, in particular citrullinated proteins in RA. They will also evaluate the therapeutic potential of dendrimers in RA experimental models based on preliminary presults and characterize at a fundamental level the molecular targets of these compounds on immune cells. The team will also provide an interface between fundamental research conducted in team 2/3 and clinical research in the department of rheumatology in Toulouse hospitals enabling clinical trials. It will provide access to patient material for therapeutic approaches and conduct in collaboration with team 2 immunotherapeutic approaches based on the specific elimination of anti-ACPA autoantibodies. Generally, while these research topics represent important new approaches in RA research to solidify results obtained during the last research term and extend them to clinical applications, the autonomy of this team is at present not fully established. It appears heterogenous in constitution and the full independence of this team, as compared with team 2 and regarding the research to be conducted is at present, after two years of existence, not formally established.

The team is comprised of researchers with heterogeneous backgrounds. Not all of them have recently worked on RA. A large part of the 43 articles are collaborative, through the clinical ward and the work published in the area of fundamental research, although correct, does not include work published in the field of RA. It is difficult to point

out to research orientations through the analysis of the published work. Most partnerships are local, regional and national.

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

Due to the only recent constitution of part of the group, the impact generated is at present modest. To be noted are 16 presentations at international meetings and no international invitations. This team will be newly reconstituted by the merger of independent groups, a track record of recruitment does not exist yet. The committee members were not able to evaluate the ability of the team to raise funds, to successfully apply for competitive funding, and to participate to scientific and industrial clusters.

2 patents have been applied for on dendrimers (immunomodulatory synthetic compounds).

- **Appreciation on the project:**

The proposed project includes three parts: (1) citrullin immunization enhanced arthritis models, (2) Immunointervention with dendrimers and (3) Clinical research. Part 1 would be more interesting if it was citrullin-triggered arthritis models. Part 2 might be interesting. Part 3 can provide outstanding data if specific anti citrullin immunosuppression is evaluated.

- **Conclusion:**

— Overall appreciation :

At this point, the project appears not to be established in firm ground. However, it may turn quite successful if any kind of citrullin induced arthritis model develops or if dendrimers confirm some activity, or, most important of all, if the clinical team successfully runs a trial of anti citrullin suppression in rheumatoid arthritis patients.

— Strengths and opportunities :

This is a Team whose strength is its clinical link. It may turn critical to the development of citrullin immunity suppression therapy in RA.

— Weaknesses and threats :

Dendrimers are potentially an interesting contribution to the treatment of RA. If the team can develop arthritis models in the mouse and treat them successfully with dendrimers, it may turn out to be very interesting. So, the next two years will be very critical for this team.

— Recommendations :

The team is at present only partially constituted, existing as a JE2510 since 2007. It is composed of researchers with different backgrounds that will join to work on new experimental and clinical approaches in RA research. While the clinical interface appears to be built on a solid background, the feeding-in of the experimental approaches awaits confirmation. After two years of existence the true autonomy of this research team and its team leader from team 2 has not been formally established and awaits confirmation. While this team could be given a chance to be fully independent, it can also be merged with team 2.

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 : *KERATINOCYTE DIFFERENTIATION AND EPIDERMAL BARRIER*

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 : *AUTOANTIBODIES TO CITRULLINATED POTEINS*

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 : *EXPERIMENTAL PATHOLOGY AND NEW TREATMENTS IN RA*

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

Université Paul Sabatier
TOULOUSE III
Faculté de Médecine PURPAN

UNITÉ MIXTE DE RECHERCHE 5165

"Différenciation Épidermique et Autoimmunité Rhumatoïde"

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Toulouse, le 26 mars 2010

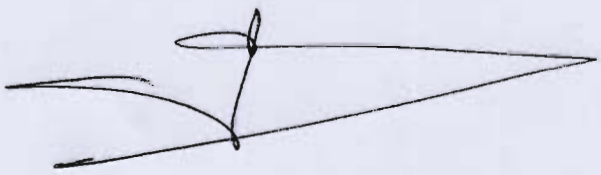
Objet : Pré-rapport AERES (évaluation UMR5165 – UDEAR)
Nos réf : GS/CP 064/10

Monsieur le Directeur,

Pour faire suite à la réception du pré-rapport établi par le comité d'évaluation AERES relatif à l'examen de notre projet d'unité, et comme demandé, je vous informe que nous n'avons pas d'observation de portée générale à formuler.

Veuillez recevoir, Monsieur le Directeur, mes cordiales salutations.

Pr Guy SERRE
Directeur



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