Inflammation, chimiokines et immunopathologie

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Cytokines, Chemokines, and Immunopathology

Under the supervision of the following institutions and research bodies:

Université Paris-Sud

Institut National de la Santé Et de la Recherche Médicale - INSERM

December 2013

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

Department for the evaluation of research units

On behalf of AERES, pursuant to the Decree of 3 november 2006[1]*,*

– Mr. Didier HOUSSIN, president
– Mr. Pierre GLAUDES, head of the evaluation of research units department

On behalf of the expert committee,

– Ms Brigitte AUTRAN, chair of the committee

[1] The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n ° 2006-1334 of 3 November 2006, as amended).

Evaluation report

This report is the result of the evaluation by the expert committee, the composition of which is specified below. The assessments contained herein are the expression of an independent and collegial deliberation of the committee.

Unit name:	Cytokines, Chemokines, and Immunopathology
Unit acronym:	
Label requested:	UMR_S
Present no.:	UMR_S996
Name of Director (2013-2014):	Mr Marc PALLARDY
Name of Project Leader (2015-2019):	Ms Françoise BACHELERIE

Expert committee members

Chair:	Ms Brigitte AUTRAN, Université Pierre et Marie Curie, Paris
Experts:	Mr Laurent ANDREOLETTI, Université de Reims (representative of CSS Inserm)
	Ms Chantal DESDOUETS, Institut Cochin, Paris
	Mr Gerard GRAHAM, Glasgow University, Glasgow, United Kingdom
	Mr Moncef GUENOUNOU, Université de Reims (representative of CNU)
	Ms Stéphanie HUGUES, Geneva University, Geneva, Switzerland
	Mr Abdelhadi SAOUDI, Centre de Physiopathologie de Toulouse Purpan
	Ms Claudine SCHIFF, Centre d'Immunologie de Marseille-Luminy

Scientific delegate representing the AERES:

Mr Joost VAN MEERWIJK

Representatives of the unit's supervising institutions and bodies:

Mr Jean-Jacques GIRERD, Université Paris-Sud

Ms Laurence PARMANTIER, Inserm

Mr Christian POUS (representative of Doctoral School n°425)

1 • Introduction

History and geographical location of the unit

The UMR 996 unit is the continuation of INSERM UMR 764 created in 2006 (contract 2006-2009) and was formerly directed by Mr Dominique EMILIE until his sudden death in 2011. Mr Marc PALLARDY has headed it during the last two years with the contribution of Ms Françoise BACHELERIE. The overall scope of the unit is the study of mechanisms involved in immunopathology and inflammation.

During the last term, five teams jointly investigated the patho-physiology of immunological and inflammatory disorders, in order to identify potential therapeutic targets.

For the following term, four teams will follow this original goal with common interests in the molecular mechanisms regulating host susceptibility and response to inflammatory, immune, and infectious diseases, with a continuum from genes to animal in vivo studies and human analyses in the context of:

- team 1: chronic immune stimulation and host susceptibility factors (including CXCR4) during persistent infections, immunodeficiencies and cancers,

- team 2: allergies induced by adjuvants and chemical or drug agents and autoimmune diseases,

- team 3: inflammation of the liver due to metabolic disorders (alcohol intake and obesity) taking into account the role of the intestinal microbiota,

- team 4: the role of chemokine receptors (including CXCR4) in immunodeficiency, autoimmunity and cancer associated with disorders of leukocyte migration.

The unit is localized on two sites: in an INSERM facility close to the Antoine Béclère University Hospital in Clamart (teams 1, 3 and 4) and in the Faculty of Pharmacy (University Paris-Sud) in Châtenay-Malabry (team 2). The two locations are distant by 5 km representing a 15 minutes drive by car.

The unit is belonging to the Institut Fédératif IPSIT "Institut Paris-Sud d'Innovation Thérapeutique" allowing access to 8 technical research platforms and Ms Françoise BACHELERIE is the deputy director of the IPSIT Institute.

Management team

Mr Marc PALLARDY and Ms Françoise BACHELERIE successfully helped the UMR996 unit overcome the trauma of Mr Dominique EMILIE's passing and maintained the good quality of research characteristic of this unit.

Ms Françoise BACHELERIE is the candidate for heading the unit during the next term.

The unit is composed in 2013 of four teams gathering about 67 persons including 44 permanent staff scientists from INSERM and from CNRS, Teacher/Researchers from the Medical and from the Pharmacy Schools of Université Paris-Sud, including Clinicians.

UMR 996 has set up the following management organization: a monthly meeting of the teams' heads and the administrative manager of the unit to discuss e.g. budget, equipment, and student recruitment. The permanent scientific staff is always consulted on strategic decisions.

The general assembly is gathered at least once a year for budget approval and when needed for any request from the staff.

The budget depends on INSERM and university allowance and on external grants. It is established per team and part of the resources is pooled for the common laboratory expenses and for strategic decisions (15 % contribution from all grants): equipment, young investigators or emerging projects.

In addition, 5 % of university budget allowance was given each year to the Institut Fédératif de Recherche (IPSIT) for access to platforms.

AERES nomenclature

SVE1_LS6 Immunology, microbiology, virology, parasitology

SVE1_LS4 Physiology, pathophysiology

SVE1_LS7 Clinical research, public health

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	8	8
N2: Permanent researchers from Institutions and similar positions	15	12
N3: Other permanent staff (without research duties)	8	8
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	5	3
N6: Other contractual staff (without research duties)	7	3
TOTAL N1 to N6	**44**	**34**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	17	
Theses defended	17	
Postdoctoral students having spent at least 12 months in the unit*	1	
Number of Research Supervisor Qualifications (HDR) taken	13	
Qualified research supervisors (with an HDR) or similar positions	19	18

2 • Overall assessment of the unit

Overall, the good scientific quality of the unit is characterized by discoveries of new mechanisms, focusing mainly on the chemokine receptor CXCL12/CXCR4-7 axis, chemical sensitizers and intestinal microbiota, in a broad variety of inflammatory, allergic, auto-immune or alcoholic/non-alcoholic liver diseases and of immunodeficiency diseases. These successes result from the ability of the various teams to develop excellent basic and translational researches strongly linked to the university hospital and highly efficacious collaborations in the Pharmacy sector and industry. Despite the relatively small size of each team, productivity has been good with some high quality, but not outstanding, publications assessing the highly recognized reputation of the team, which should be strengthened by

lectures in international conferences. The attractiveness of the unit is also supported by an impressive series of external collaborations, patents, coordination of large local or international highly competitive programmes and a capacity to generate strong financial support. Most of the unit's researchers are strongly involved in higher education, training through research and produce key expertise for regulatory bodies in public health institutions. These achievements are a strong asset for the next five-year research programme which is relying on several solid and innovative findings and should prove to be as productive. Overall, the multiplicity of projects in each team might, however, jeopardize the scientific outputs during the next period that would benefit from a clearer strategy to prioritize on the most promising projects to reinforce internal collaborations and to recruit full-time experienced researchers.

Strengths and opportunities related to the context

High impact publications with good international recognition and visibility despite a lack of publications or invitations in major journals and international meetings.

Solid interactions with medical and pharmaceutical organisations.

Good reputation of the unit leader based on a 10 year-old breakthrough and on solid recognition of the other team leaders.

Definitely the strongest points of the unit are:

- very high level of interactions with Regulatory bodies at high decisional level;

- numerous patents and collaborations with the industry;

- very strong Involvement in training through research of the whole unit.

Overall good five-year plan projects in each team particularly in teams 1 & 3, which developed relatively well focused projects, and some good projects in the two other teams despite a multiplicity of small sub-projects.

Weaknesses and threats related to the context

Few invitations in international meetings limiting the unit's international visibility.

Relatively poor organisation and life of the unit with lack of scientific advisory board, lack of systematic analysis of potential internal collaborations in research projects and lack of a clear strategy in expanding the strongly limited human resources.

Weaknesses in the strategic five-year plan with:

1) lack of clear unifying strategic scientific plan despite an effort to focus on chemokine/chemokine receptors;

2) Multiplicity of small sub-projects in each team that jeopardize their strengths and chances of success due to the small size of each team.

Few internal collaborations.

Recommendations

- to set up an External Scientific Advisory Board to help to prioritize and refocus on the best projects in each team;

- to strengthen interactions within and between teams;

- to recruit more young full time scientists.

3 • Detailed assessments

Assessment of scientific quality and outputs

Overall, the good scientific quality of the unit is characterized by its recent discoveries of some new mechanisms and pathways of inflammation or immunopathogenesis in a broad spectrum of inflammatory, allergic, auto-immune or alcoholic/non-alcoholic liver diseases and of immunodeficiency diseases. These successes result from the ability of the various teams to reasonably combine their efforts by focusing on two molecular axes from the host inflammatory pathways, including the chemokine receptors (mainly the CXCL12/CXCR4-7 axis) and a glucocorticoid receptor (GILZ), and on two external factors, chemical sensitizers and intestinal microbiota. There is an excellent focus of all groups on translational research.

Despite the relatively small size of each team and the multiplicity of projects, productivity has been good with some high, but not outstanding, quality publications in 'Blood' and the 'Journal of Clinical Investigation', and notable contributions to e.g. CXCR4 and CXCR7 biology, representing major achievements largely driven by teams 1 and 4.

They also set up an impressive series of external collaborations, particularly with the industrial sector, that lead to several patents and strong financial support from the industry.

Assessment of the unit's academic reputation and appeal

The good academic reputation of the unit is based on a good track record of publications, but is limited as assessed by the lack of invitations in major international meetings.

The strong appeal of the unit members is assessed by their role as coordinator and/or their involvement in recently appointed major local, national, and international networks, in particular as partners of:

- several "Investissements d'Avenir":

- LABEX LERMIT “Laboratory of Excellence in Research on Medication and Innovative Therapeutics”. The unit’s current director is member of the steering committee and of the “Maturation and early drugability group” and in charge of the educational program. Two other team-chiefs are members of the LERMIT council, one is also member of the “Project call“ research group and one is the co-coordinator of the “T2 research project”;

- EQUIPEX project allowing access to the innovative “mass cytometry” technology;

- the new IDMIT Center (National Center for Infectious Diseases Models and for Innovative Therapies).

- DHU “Départements Hospitalo-Universitaires” recently created by AP-HP: DHU “TORINO: Thorax innovation” for team 2 and DHU “Hepatinov” for team 3;

- the five-year/38 partner/34.9 M€ EU-IMI (Innovative Medicine Initiative) ABIRISK “Anti-Biopharmaceutical Immunization: prediction and analysis of clinical relevance to minimize the RISK” project (unit’s director).

In addition the unit’s attractiveness is assessed by its capacity to recruit highly qualified postdoctoral researchers.

Assessment of the unit's interaction with the social, economic and cultural environment

This aspect is one of the highlights of UMR 996, which has shown a strong involvement in technology transfer with several patents. All teams have set up numerous collaborations with the industrial sector and big pharmaceutical companies.

This strong major involvement in collaborations with the pharmaceutical industry is emphasized by the coordination of the ABIRISK IMI network and involvement in the LERMIT Labex (see above), which will both give them strong opportunities for breakthroughs in the next five years.

Assessment of the unit's organisation and life

The unit has set up an appropriate organization with monthly meetings of the teams' heads and the administrative manager to discuss budget, equipment and student recruitment. The permanent scientific staff is consulted on strategic decisions and the general assembly is gathered at least once a year for budget approval. The budget depends on INSERM and university allowance and on external grants. It is established per team and part of the resources is pooled for the common laboratory expenses and for strategic decisions.

In addition, 5 % of university budget allowance was given each year to the Institut Fédératif de Recherche (IPSIT), of which the future unit's director is vice-chair, thus allowing access to the eight research high-tech platforms.

However the experts committee is concerned by the lack of an external scientific board and of a scientific policy to define strategic scientific orientations or help teams in difficulty at re-orienting their projects. Although one of the new programme aspirations is to strengthen synergy between teams and coherence of the scientific perspectives, the evaluators were not convinced by the capacity of the future unit's organisation to favour cohesion and coherence among a too broad variety of projects that jeopardize the unit's strengths.

Furthermore, the scientific life and organization of the unit is limited by its localization on two distant sites, a problem that will be solved at the end of the next term, by reunification in the Faculty of Pharmacy.

Finally there is no strong internal incentive to favour interaction between scientists or to help solve the staff's acute needs linked to the paucity of full time researchers or the lack of permanent technical staff.

Assessment of the unit's involvement in training through research

A major strength of the unit is its strong involvement in the organisation of higher education. Most of the researchers are Professors or Assistant-Professors at the Faculty of Medicine or Pharmacy and two team-chiefs are members of the steering committee of the Université Paris-Sud.

In addition, the four teams are part of the Doctoral School "Innovation Thérapeutique: du Fondamental à l'Appliqué" and its governance, as well as in active medical and nurses training.

Assessment of the strategy and the five-year plan

Altogether the past unit's research accomplishments have paved the way for high quality future research programmes. The four teams of the future unit tentatively set up an ambitious programme to further understand some of the immune mechanisms of a variety of inflammatory, auto-immune, allergic diseases and immunodeficiencies they recently described, with a real effort to focus upon two axis of the CXCR4/CXCR7 chemokine receptors and of the GILZ glucocorticoid receptor. Each of the teams, most of them being relatively small and lacking full time researchers, has developed several research projects involving these two axes.

The unit has set up an impressive number of original animal models that should allow them to explore the basic mechanisms involved in the various pathogeneses they wish to explore, while analysing in parallel the validity of these mechanisms in human and patient-samples to which they have a large access. In addition, their ability to conduct state of the art experimental investigations is assessed by their good access to technological facilities and their demonstrated capacity to raise substantial funding.

However the multiplicity of the fields studied by this small unit has limited its ability to produce novel breakthroughs. There is no clear strategic plan for this relatively small unit. The topics covered within each team appear extremely diverse, with a lack of focus and little unifying science within and between each team despite efforts to concentrate on the two common axes of research but in a broad range of cellular and pathological contexts.

4 • Team-by-team analysis

Team 1: Immunoregulation, Chemokines, and Viral Persistence

Name of team leader: Ms Françoise BACHELERIE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	5	4
N3: Other permanent staff (without research duties)	1	
N4: Other professors (PREM, ECC, etc.)	1	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	
N6: Other contractual staff (without research duties)	2	
TOTAL N1 to N6	**12**	**5**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	6	5

• Detailed assessments

Assessment of scientific quality and outputs

Strong scientific output developing a 10 year-old breakthrough on the role of the CXCL12/CXCR4-7 axis in various immunodeficiencies (e.g. the WHIM syndrome) and infectious diseases (HPV infection, filariasis), and with

original descriptions of the role of the GATA2 transcription factor as a new predisposing factor for myelodysplastic syndromes, and of new immunoregulatory molecules (GILZ and TRPM4) in inflammation and tolerance.

The team produced several cutting edge original gene-modified mouse models of great potential for the WHIM syndrome to investigate CXCL12/CXCR4-7 antagonists or the role of the CXCL12/CXCR4-7 axis in filariasis, as well as models to study the interplay between the CXCL12/CXCR4-7 axis and GATA2 transcription factor, while developing the French WHIM patient cohort to be included in a future NIH-clinical trial.

Very solid scientific production including 15 high Impact publications with an IF>10.

Assessment of the team's academic reputation and appeal

Overall, the good reputation of the team's leader is assessed by her regular participation/invitation to national and international meetings despite lack of invitation in high impact international conferences. In addition, the team's researchers and leader are regular peer reviewers for well-established international journals.

The team's strong appeal is assessed by a very good financial support with 25 national grants mainly from public and associative national sources, participation and/or coordination to local and national "initiatives d'excellence" (Labex LERMIT, Equipex FlowCytech, IDMIT) as well as EU programmes (E-Rare, IMI-ABIRISK)

Assessment of the team's interaction with the social, economic and cultural environment

The strong contribution of the team to its environment is assessed by a solid intellectual property protection with four patents, by its regular consulting services for private companies, by its participation to several clinical trials, to publications in professional and technical journals and textbooks, to regulatory agencies as well as to the implementation of standards and guidelines.

Assessment of the team's organisation and life

The profound reorganization of the team after its former leader's accidental death has allowed introduce strong new scientists and expertise but has delayed the development of some programs. The team leader is deputy director of the IFR141-IPSIT and is a member of local steering committees (School of Medicine, LERMIT, FlowCytech, IDMIT).

However the team is limited by its small size with 2,4 FTE including 3 assistant-professors and the lack of postdoctoral researchers, research technicians or engineers to support the research activities. In addition, despite some collaborations with other teams of the unit, the there is no clear strategy in the interactions to be set within the rest of the unit nor in the reinforcement of human resources.

Assessment of the team's involvement in training through research

The team members are heavily implicated in teaching activities and in the organization of teaching for Master and PhD degrees and involved in the Doctoral School "Innovation et thérapeutique: du fondamental à l'appliqué".

Since 2008, the team trained six Master-, two PhD-, and one EPHE-students and is currently supervising four Master degrees and three PhD-students since 2011.The quality of the doctoral theses is assessed by publications with students in prominent position.

Assessment of the strategy and the five-year plan

The team proposes an ambitious project subdivided in four parts with pathophysiological and therapeutic orientations. The proposed project is well constructed and ambitious and builds upon promising preliminary data achieved in the previous contract. Overall the proposal is coherent, focusing on the CXCL12 and GILZ axes and their molecular interplay between receptors, studying their implication in chronic immune activation-associated diseases (cancer and HPV infection) as well as new therapeutic strategies. However several other research objectives such as the identification of new markers of skin-specific Treg cells aiming and potential therapeutic targets might jeopardize the strength of this small team.

Nevertheless several original tools and mouse models as well as established relevant collaborations are obviously an asset for the success of the project. However, the project would benefit from being more focused in order to increase its chances of success, particularly the project described in part three.

Conclusion

- **Strengths and opportunities:**

- strength and originality of the project (CXCL12/CXCR4-7 axis in the WHIM syndrome and HPV infection);

- development of tools and experimental settings to investigate the contribution of CXCR7 to CXCL12/CXCR4 functions;

- very good scientific productivity with some publications in high impact journals;

- good attractiveness of the team for PhD students;

- strong national and international collaborative network;

- good international scientific visibility;

- good capacity to obtain grants.

- **Weaknesses and threats:**

- the team members have only few invitations to plenary lectures in international meetings;

- the group has shrunk significantly. The size of the team is thus modest to achieve all the objectives listed. The number of post-doctoral fellows (especially international ones) and perhaps PhD students is not sufficient;

- lack of experienced researcher, postdoctoral researchers, research technicians, or engineers;

- lack of clear specific strategy for connection with institutional organisms for the HPV project.

- **Recommendations:**

- to limit the number of projects (in particular the Treg project which appeared as the weakest among the team's ones) and to prioritize research objectives (as an example refocus on the WHIM syndrome and the HPV project which appear to be promising) in order to remain competitive;

- to move from national recognition to international visibility;

- to strengthen its manpower by increasing the number of tenured positions (technicians or engineers) and to recruit postdoctoral researchers;

- to favour efficient synergy with others teams of the unit sharing complementary expertise and scientific questions.

Team 2: Drug and Chemical Allergy, Immunotoxicology, and Immunopathology

Name of team leader: Mr Marc PALLARDY

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	3	3
N2: Permanent EPST or EPIC researchers and similar positions	6	3
N3: Other permanent staff (without research duties)	3	3
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	
N6: Other contractual staff (without research duties)	2	2
TOTAL N1 to N6	**15**	**11**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	7	
Theses defended	10	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	5	5

• Detailed assessments

Assessment of scientific quality and outputs

Quality of the scientific production is good. It is based on the analysis of various aspects of inflammation and allergy, with a particular strength of the Nrf2 research focusing on the mechanism of inflammation caused by the alum vaccine-adjuvant with relevant collaborations with the academic and industrial sector, a reasonable production on the role of neutrophils in chemical allergy and regulation of inflammatory responses but a weaker impact of the research on T cells specific for drugs involved in allergic reactions.

Assessment of the team's academic reputation and appeal

Overall national and international visibility is good and has high impact in the toxicology field of the Team leader. There is also a strong international leadership of a highly funded EU programm in partnership with the industry. However, the team's reputation and appeal is somewhat limited with a lack of invitations in international meetings and of recruitment of young world-class researchers.

Assessment of the team's interaction with the social, economic and cultural environment

A major strength of the team is its strong and numerous interactions at high national and international levels with industry and with regulatory bodies and its contribution to national and international guidelines in the field of toxicology and therapeutics of allergy and vaccines.

Assessment of the team's involvement in training through research

Another strength of the team is its major involvement in teaching and training through research, in the steering committees of doctoral school and university governance.

Assessment of the strategy and the five-year plan

The team proposes pursuing its previous research programm along three research axes on:

I) the well focused Nrf2 project with solid background in the exploration of the role of Nrf2 in chemical allergy and vaccine adjuvants,

II) the regulation of inflammatory responses by neutrophils, particularly on the role of neutrophil extracellular traps and glucocorticoid-induced leucine zippers (GILZ), in immediate and delayed hypersensitivity and in inflammation and acute respiratory syndrome;

III) the identification of drug-specific naïve T cells involved in allergic reactions. The last axis however appeared largely speculative and risky.

The chances of success of the project are supported by the team's original mouse models, new technologies, and relevant collaborations as well as by the high impact EU and local pharmacology programms the team coordinates or is involved in. However, the experts committee feels that the range of programmes is too broad, while the feasibility and the pertinence of the NET programme and of axis three are weak.

Conclusion

- **Strengths and opportunities:**

- strength and originality of the Nrf2 project;

- the team's original mouse models and new technologies;

- relevant collaborations, particularly with the industrial sector;

- high impact programs;

- high visibility in the toxicology field;

- strong involvement into higher education and doctoral school;

- major involvement and recognition in social environment (regulatory agencies and industrial sector).

- **Weaknesses and threats:**

- multiplicity of projects for a small team;

- weakness of the highly speculative emerging project on neutrophil extracellular traps;

- weak pertinence and feasibility of axis 3;

- few internal and intra-unit collaborations.

- **Recommendations:**

- to set up a clear scientific strategy refocusing on the most promising projects;

- to set up strong internal and intra-unit collaborations;

- to attract full time researchers.

Team 3 : Intestinal Microbiota and Macrophages in Liver Inflammation

Name of team leader: Mr Gabriel PERLEMUTER

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	2	2
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1
N6: Other contractual staff (without research duties)	1	
TOTAL N1 to N6	**5**	**4**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

Despite its small size (composed of eight persons), the team and its leader have a strong expertise in the field of inflammatory mechanisms involved in liver damages related to overweight (NAFLD, non-alcoholic fatty liver disease) and alcoholic liver disease (ALD) thanks to its strong association with the department of Gastroenterology, Hepatology and Nutrition of the Béclère University Hospital. The past four-year research program was well focused and produced major achievements with the identification of the key role of the CXCL12/CXCR4 axis in obesity-related liver inflammation, of GILZ as a regulator of inflammation in Kupffer cells, and of intestinal microbiota in ALD and in obesity-induced liver diseases, with several strong papers in good impact specialized journals (Gastroenterology, Hepatology, J. Hepatology, Gut).

Assessment of the team's academic reputation and appeal

Although this young team has not yet gained strong international visibility, it is highly respected and has a recognized expertise in the field with frequent invitations to relevant meetings. It has developed numerous and relevant collaborations with local and national teams and coordinates the DHU (Département Hospitalo-Universitaire) "Hepatinov" allowing development of translational research. The team has also demonstrated a very good capacity to raise national and international funds.

Assessment of the team's interaction with the social, economic and cultural environment

The team leader has skills to develop academic and hospital interactions with the DHU and strong collaborations with pharmaceutical companies.

Assessment of the team's involvement in training through research

The team and its leader are strongly involved in higher education for medical students and nurses. Their important activity in training through research is assessed by the supervision of 11 Master-degree students and 3 PhD theses with good publication levels in the last four years while currently supervising three more PhD students.

Assessment of the strategy and the five-year plan

The project has a well-balanced mix of state-of-the-art mouse models with a clear relevance to human liver diseases. The team has reasonable preliminary data identifying specific microbial species predisposing to excessive inflammation. The proposed experiments are a logical continuation from the obtained results. The project will focus on inter-connected themes studying the role of the CXCL12 and GILZ axis and of the intestinal microbiota in liver inflammation and immune dysfunction in liver inflammatory diseases linked to alcohol and obesity.

Altogether, the team's combined basic/translational research and key local and external collaborations put it in arobust position to continue in the next period along a cohesive research programme.

Conclusion

- **Strengths and opportunities:**

- good expertise in the proposed line of research;

- strong capacity to produce significant scientific outputs;

- appropriate combination of basic and translational research will help contribute maximally to the field;

- strong external and internal collaborations supporting the viability of the studies.

- **Weaknesses and threats:**

- a small group in a highly competitive field;

- multiplicity of projects is a real danger for this small and young team;

- number of scientists dedicated per project may not be adequate.

- **Recommendations:**

- a new staff member should be recruited in the near future;

- if recruiting a new staff-member is not possible, the team will certainly have to make choices and prioritize certain themes;

- more presentations at international meetings would also be good to increase international visibility.

Team 4: Disorders of Lymphocyte Trafficking, Chemokines, and Innovative Therapeutics

Name of team leader: Mr Karl BALABANIAN

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	2	2
N2: Permanent EPST or EPIC researchers and similar positions	3	2
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	2
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**7**	**7**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	4	
Qualified research supervisors (with an HDR) or similar positions	5	5

• Detailed assessments

Assessment of scientific quality and outputs

This team successfully developed an original project on the role of chemokine receptor CXCR4 in disease development associated with rare immune-deficiency disorders of leukocyte migration, by combining investigations in human and mouse models. The team produced several scientific outputs on CXCR4 function in the WHIM Syndrome in collaboration with the unit's leader and team 1 and in Idiopathic CD4+ T-cell Lymphocytopenia, on CXCR7 and CCR1 in Systemic Lupus Erythematous, and on the CXCL12-CXCR4 axis in cancer. Collaboration with the industrial sector allowed the team to propose a chemokine-receptor antagonist as a new therapeutic target. Altogether, this scientific production was associated with a good publication record in good general or specialized strong impact journals.

Assessment of the team's academic reputation and appeal

Overall high impact publications have been shared with team1 but, without invitations in international meetings, the team's visibility is still limited. Nevertheless, the team's expertise is well recognized as assessed by numerous national and international collaborations allowing high number of co-authoring publications while the team leader is active in peer-reviewing for international journals. The team has set up several medical collaborations and is involved in clinical trials and cohort organisation. It is also part of the LABEX LERMIT, member of the LERMIT council and co-coordinator of one Labex project. The team's scientific attractiveness is also assessed by its capacity to recruit a very promising post-doctoral researcher who should greatly improve the research power of this small team. The team leader has shown strong ability to obtain significant national and international grants.

Assessment of the team's interaction with the social, economic and cultural environment

The team leader has set up strong animation activities in the scientific field and serves as an expert for national and international evaluations. The team leader has licensed the design, characterization and application of the mouse model of the WS.

Assessment of the team's involvement in training through research

The team is strongly involved in the education/teaching programs of the Université Paris-Sud and in the doctoral school. Its huge training activity for young investigators is assessed by the supervision of 14 Master- and seven PhD-students with good level publications for the majority of the PhD theses.

Assessment of the strategy and the five-year plan

The team's translational research project aims at developing novel drugs to target inappropriate migration of immune cells, with a special focus on chemokines and their receptors and their related intracellular partners. It proposes to extend the CXCR4 theme further to two human rare immunodeficiencies. Team 4 also plans to examine aspects of autoimmune and malignant B cell-biology with many goals for each section.

Altogether the WHIM syndrome and ICL project is persuasive but some of the approaches proposed are not supported by solid evidence (particularly the iPS cells) and it seems unlikely that this small group will develop therapeutics in this highly competitive field. The autoimmune B cell-theme is not supported by team's track record in this competitive area (apart from the newly recruited post-doc) while the malignant B cell-project seems to be risky and is therefore not strongly persuasive.

Conclusion

- **Strengths and opportunities:**

- high quality and good attractiveness of the team leader with scientific competence, enthusiasm, great ability to obtain financial support, establish internal and external collaborations, perform scientific animation, and teach;

- innovative project is based on complementary skills of newcomers.

- **Weaknesses and threats:**

- suboptimally focused proposals, some based on tenuous and not persuasive scientific links;

- many goals for each section with a number of persons involved in each program too low to efficiently address the different questions during a five-year period;

- no clear strategy to recruit post-doctoral scientists.

- **Recommendations:**

- to prioritize on the most promising projects such as the strong CXCR4 axis oriented towards stem cells and the plasma cell project while the CD5 project should interact more with the CXCR4 axis and/or focus on Waldenström's disease;

- to develop more interactions between the groups of the team;
- to recruit post-doctoral scientists and senior researchers;
- to limit the number of collaborations that do not favour scientific visibility.

5 • Conduct of the visit

Visit date:

Start: Tuesday, December 3rd 2013 at 08.00 am

End: Tuesday, December 3rd 2013 at 06.00 pm

Visit site:

Institution: Inserm UMR 996, Béclère Hospital

Address : 157 rue de la Porte de Trivaux, 92140 Clamart

Conduct or programme of visit:

08.00 am	Closed-door meeting: expert committee members and scientific delegate (DS) of the AERES (Mr Joost VAN MEERWIJK)
08.30 am	Presentation by the head of the unit (Ms Françoise BACHELERIE and Mr Marc PALLARDY): past activity and projects
09.00 am	Team 1 Immunoregulation, chemokines and viral persistence (Head: Ms Françoise BACHELERIE)
09.45 am	Team 2 Drug and Chemical Allergy, Immunotoxicology and Immunopathology (Head: Mr Marc PALLARDY)
10.30 am	Coffee break
11.00 am	Team 3 Intestinal microbiota and macrophages in liver inflammation (Head: Mr Gabriel PERLEMUTER)
11.45 am	Team 4 Disorders of lymphocyte trafficking, chemokines and innovative therapeutics (Head: Mr Karl BALABANIAN)
12.30 pm	Lunch-buffet
01.30 pm	Meeting of the experts committee with representatives of the Université Paris-Sud and Inserm: • Prof. Jean-Jacques GIRERD, Vice Président, Université Paris-Sud • Ms Laurence PARMANTIER, head of Paris Sud Inserm delegation • Prof. Jean-Charles DUCLOS-VALLÉE, faculty of Medicine
02.00 pm	Meeting of the experts committee with a representative of the "Therapeutic Innovation Doctoral School" (ED n°425) of the Université Paris-Sud • Prof. Christian POÜS, head of the "Physiopathology" axis
02.15 pm	Three parallel meetings of the experts committee with: • PhD students and postdoctoral fellows • Engineers, technicians and administrative assistants • Researchers with permanent position (except the unit's director and team-chiefs)
03.00 pm	Closed-door meeting of the experts committee and AERES representative with the unit's directors, Ms Françoise BACHELERIE and Mr Marc PALLARDY
03.30 pm	Tea-break
04.00-06.00 pm	Closed-door meeting of the experts committee members and DS

6 • Supervising bodie's general comments

UNIVERSITÉ PARIS SUD

Comprendre le monde, construire l'avenir®

Le Président de l'Université Paris-Sud

à

Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
AERES
20, rue Vivienne
75002 Paris

Orsay, le 24 mars 2014

N/Réf. : 67/14/JB/LM/AL

Objet : Rapport d'évaluation d'unité de recherche
N° S2PUR150007524

Monsieur le Directeur,

Vous m'avez transmis le 3 mars dernier, le rapport d'évaluation de l'unité de recherche INFLAMMATION, CHIMIOKINES ET IMMUNOPATHOLOGIE - n° S2PUR150007524 et je vous en remercie.

L'université se réjouit de l'appréciation portée par le Comité sur cette unité et prend bonne note de ses suggestions, notamment en ce qui concerne la mise en place d'un comité scientifique externe.

Vous trouverez en annexe les éléments de réponse de Monsieur Marc PALLARDY, directeur de l'unité de recherche et Madame Françoise BACHELERIE, candidate à la direction de l'unité de recherche.

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

UNIVERSITÉ PARIS SUD PRÉSIDENCE Bâtiment 91405 ORSAY cedex

Jacques BITTOUN
Président

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INSERM UNITE 996
Inflammation, Chimiokines & Immunopathologie
Unité Mixte de Recherche INSERM - Université Paris-Sud – Labex LERMIT – Hôpital Antoine Béclère
Professeur Marc Pallardy
Directeur
Docteur Françoise Bachelerie
Candidate à la direction

Clamart, le 16 mars 2014

Comité AERES du 3 décembre 2013

OBSERVATIONS DE PORTÉE GÉNÉRALE

The unit and teams' heads thank the experts of the AERES Committee for their analysis of the assessment of the "Cytokines, Chemokines, and Immunopathology" unit and their recommendations in the context of the creation of the "Inflammation, Chemokines and Immunopathology" unit.

To strengthen interactions within and between teams is a major aspiration of the unit's program as the committee noticed. The committee is expecting "high quality future research programs" from the unit's accomplishments and its recommendation to prioritize on some projects in each team with the help of an External Scientific Advisory Board will certainly contribute to pursue this goal.

To maintain the unit's attractiveness and especially to recruit postdoctoral fellows and young full time scientists is also a major objective of the unit and teams' heads and is specially challenging in this period of job and funding scarcity. This a conducted strategy for all teams recently illustrated with the recruitment in Team 3 of a postdoctoral fellow, in Team 4 of a senior fellow who will be supported by the unit for an academic recruitment as a full time scientist, and in Team 2 of a young assistant professor in toxicology starting in September 2014.

Team1 will also pursue recruiting postdoctoral fellows and engineers in order to increase its workforce and remain competitive and strengthen its collaboration with Paris XI hospitals and its focus research effort within the members of the team and also with the 3 other teams.

To prioritize research objectives will also be a goal of Team 2. As noticed by the committee the Neutrophil Extracellular Traps-related project bloomed from a relatively emerging concept, the pertinence of which is supported by more than 400 PubMed citations since 2004. This project developed in the context of the anaphylactic shock is clearly translational and its feasibility relies on strong collaborations with clinicians and on institutional organisms' financial supports. Recent results of the Team identifying 5 new human serum albumin-derived peptides that bind penicillin

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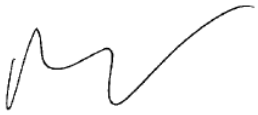
provide further evidence supporting the concept of drug-specific naive T-cells involved in allergic reactions and the feasibility of the project.

The scientific program of Team 4 notably includes developing the CD5 project within a context of industrial valorization (thus not the scale of a research project). Team 4 will pursue its research effort within the autoimmunity field, which will be strengthened by the new recruited post-doc and on two immunodeficiencies notably modeled through the development of the innovative iPS cells method with the particular aim to identify gene targets that might contribute to the development of new therapeutics.



Docteur Françoise Bachelerie
Candidate à la direction

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