Immunologie et génétique du diabète de type 1, génétique multifactorielle et endocrinologie pédiatrique

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

Immunology and genetics of type 1 diabetes, multifactorial genetics in pediatric endocrinology

University Paris 5

January 2009

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Evaluation report

Research unit:

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de l'Université Paris 5

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

January 2009

Evaluation report

The research unit :

Name of the research unit : Immunology and genetics of type 1 diabetes, multifactorial genetics in pediatric endocrinology

Requested label : UMR_S INSERM

N° in case of renewal : 561

Head of the research unit : M. Pierre BOUGNÈRES

University or school :

University Paris 5

Other institutions and research organization:

INSERM

Date of the visit :

19 janvier 2009

Members of the visiting committee

Chairman of the commitee :

M. Charles THIVOLET, University Lyon 1

Other committee members :

Ms. Anne COOKE, University of Cambridge, UK

M. Decio L. EIZIRIK, University of Brussels, Belgium

Ms Marie-Christine DE VERNEJOUL, University Paris 7

Ms. Irene NETCHINE, University Paris 6

CNU, CoCNRS, CSS INSERM, représentant INRA, INRIA, IRD.....) representatives :

M. Michel MARRE, INSERM CSS representative

M. Pierre GALANAUD, CNU representative

Observers

AERES scientific representative:

M. Pascal FERRÉ

University or school representative:

M. Bruno VARET, University Paris 5

Ms. Marie-Claude LABASTIDE, University Paris 5

Research organization representative :

M. Raymond BAZIN, INSERM

Evaluation report

1 • Short presentation of the research unit

The Unit is constituted of a total of 42 members including :

- 7 researchers with teaching duties,
- 4 full time researchers,
- 5 post-doctoral fellows,
- 10 PhD students, all with a fellowship,
- 7 technicians with a permanent position,
- 1 admnistrative assistant,
- 8 technicians or engineers with non-permanent positions.

- 10 students have obtained their PhD during the past 4 years.
- 7 members of the unit have a HDR.
- 3 members of the unit have a PEDR.
- All researchers in the lab are "publishing": 11 out of 11.

2 • Preparation and execution of the visit

The site visit was in all aspects well prepared and organized. The written documents were of high quality and described in detail the reasons for creating the new unit, as well as past, present and future research activities. The oral presentations from the two differents teams were clear and provided an excellent overview of competences and research activities. Group leaders actively participated in the discussions following the oral presentations.

Program of the visit :

09h30-10h15 : Meeting of members of the visiting committee

10h15-10h30 : Presentation of the unit project by the Director

10h30-11h45 : Team 1

11h45-13h00 : Team 2

12h35-13h00 : Discussion

13h00-13h15 : Overall summary : The Director presents the unit project; its place in the context of "Institut Paris 5" project is presented by the former Director.

13h15 : Lunch

14h15 : Meeting of the visiting Committee with administrative representatives

15h00 : Committee members meet technicians and engineers

15h20 : Committee members meet students, PhD, post-docs.

15h40 : Committee Discussion

17h15 : End of the visit

3 • Overall appreciation of the activity of the research unit, of its links with local, national and international partners

The laboratory is located at the St-Vincent de Paul Hospital, in close connection with both pediatric and adult (Cochin and Hotel Dieu) Endocrinology and diabetes departments. This ensures adequate ties between basic research and clinical activities, and the proposed unit will be strongly complementary to the clinics through its focus on type 1 diabetes (T1D) and additional endocrine disorders. This will allow the constitution of T1D cohorts (serum samples and DNA biobank). The committee members have appreciated the excellent projects from both teams, with very innovative and consistent research lines constructed step by step over the years, and not disturbed by "research fashion" or difficulties. The proposed epigenetics studies are innovative, with pertinent choices of experimental models. The planned immunology studies include new experimental models – among them several new transgenic mice - and expertises.

This new unit will be the basis for the new "Institut Universitaire de Recherche sur le Diabète Paris Descartes". Some of the members of the unit are strongly involved in teaching and doctoral formation or contribute to french scientific policy. Several members of the unit are coordinators of ANR projects.

International collaboration could be improved for both teams to provide more international visibility and lead to new collaborative projects.

4 • Specific appreciation team by team

Team 1: Immune mechanisms in type 1 diabetes

This team is composed of four groups that are nicely complementary to each other. Team 1 has made some very interesting contributions in recent years, including: (1) the characterization of the role of insulin as a key antigen in NOD mouse using proinsulin 2 -/- mice and proinsulin epitope identification to induce protection; (2) new insights in the physiology of innate and adaptive immune cells with special emphasis on the role of NKT cells to prevent autoimmune diabetes and its cooperation with plasmacytoid DCs; (3) the roles of receptor/ligand interactions in controlling NK and T cell activity and interactions between MIC in the target cells and NKG2D expressed on NK T cells and CD8 T cells but not on CD4 T cells, as well as evidences of dysfunction of the NGK2D pathway in celiac disease; (4) the development of CD8 T cell assays against peptides derived from GAD or insulin.

Publications are excellent with about 70 papers in top journals such as Diabetes, Proc. Natl. Acad. Sci., Immunity, J. Immunol, Blood, Gut. Group leaders are recognized in their fields as shown by numerous invitations in national and international meetings.

The main project concerning the study of NK cells and human type 1 diabetes will include the characterization of NK cell receptors and ligands on human islets and development of in vitro models with human cells to study the role of islet endothelium after coxsackie B4 infection. This original approach will re-assess the contribution of viral infections in autoimmune diabetes.

Concerning the role of NKT cells in the protection against type 1 diabetes, special emphasis will be put on the study of NKT-DC interactions in the pancreas upon viral infection of mice with LMCV, with focus on the contribution and tissue regulation of Tregs upon NKT cell manipulation, the nature of cellular interactions between NKT cells DC and islets.

The main projects concerning the study of T cells in type 1 diabetes will be facilitated by common and complementary strategies in mice and humans. Obtaining human specific T cells by the use of insulin specific tetramers will facilitate the screening of subjects at risk of diabetes and may allow an indirect estimation of the remaining pancreatic beta cell mass. In addition the development of new humanized animal models where mouse MHC and mouse proinsulin genes have been "knocked out" and HLA DQ8 and

human insulin introduced will provide very innovative insights into the contribution of insulin in pathogenic T cell responses.

Each of the four leaders presented innovative developments on their own projects, with clear evidence of interaction and synergy between them. Access to human material will facilitate the transfer of experimental research to humans.

Nom de l'équipe : Immune mechanisms in type 1 diabetes

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+

Team 2: Genetics and epigenetics

This team develops several studies on the importance of genetics and epigenetics in complex endocrine disorders. The rapid increase in the prevalence of early onset diabetes underlines the importance of environmental factors of type 1 diabetes. The close collaborations developed with the National Center for Genotyping CNG and with an epidemiology Inserm Unit allowed the team to explore three sources of individual variability : genotype, epigenotype and imprinting. Using a genome wide association approach in a highly selected and well-defined population of type 1 diabetic patients, the team will study individual epigenotypes at candidate loci and at the genome wide levels. The most innovative part of the project is the concept of individual "environmentome", enabling a detailed evaluation of genetic-environment interactions. A nationwide cohort of type 1 diabetic patients will hopefully enable team 2 to answer this question using mathematical models of associations in comparison to controls and healthy siblings. The adequacy of the control group appeared critical to several committee members, but the concerns presented were adequately answered by team leader.

In addition, team 2 aims to explore epigenetic variations that may explain differences in phenotypes and metabolic traits. Specific attention will concern insulin secretion and insulin action with functional genomice of PI3 kinase.

A subgroup of Team 2 will develop their studies on the biology and epigenetics of PTH signaling with identification of imprinting control elements involved in diseases such as PHP. The project was evaluated as quite competitive as it relies on a large cohort of these rare patients gained through a well established "centre de reference" and the expertise of the principal investigator of this subgroup to explore imprinting.

The team has a very good record of publications with more than 30 papers in top journals, Nat. genetics, Diabetes, Diabetes care, J. Clin. Endocr. Metab.

Nom de l'équipe : Genetics and epigenetics

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	B	B	A

5 • Appreciation of resources and of the life of the research unit

Team 1 has attracted many young and dynamic researchers in the last few years. Although developing innovative projects, Team 2 needs to attract more young researchers to guarantee its future.

Technical support in Team 1 is excellent and is a major asset for the future. However, with the exception of the animal facility, technical help is not shared between researchers for common resources such as the flow cytometry core facility. The number of PhD students, Post-docs and young researchers was very signicant for Team 1 and in contrast limited for team 2.

Committee members have noticed the absence of common seminars and shared informations between both teams. Globally, there is a demand for more information among Unit members.

6 • Recommendations and advice

— Strong points :

- The projects are innovative and consistent for both teams.
- The scientific production is excellent.
- There is a clear translational activity with a good access to clinical material and the use of a mouse to human approach.
- The unit has attracted yound and innovative researchers.
- There is a good support from the University Paris 5.

— Weak points :

- There is limited evidence of strong interactions between the two teams
- The level of international collaboration is not appropriate for the level of scientific achievements
- There is limited too information given to the staff especially to the technicians about the future of the unit and for important professional decisions.

— Recommendations :

- Interactions between the two teams must be improved, with more joint projects that will hopefully lead to more joint publications. This could be achieved through discussions and meetings between teams 1 and 2. Full time researchers could be involved in the coordination of these activities.
- An effort must be made to establish more international collaborations, and gain international support for instance through european grants.
- An effort must be made to improve the fluidity of information, possibly through regular meetings with staff representatives.
- The unit leader must care about obtaining guarantees concerning the future of the facilities.

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+

UNIVERSITÉ
PARIS DESCARTES

Le Président
Axel KAHN

Paris, le 30 mars 2009

DRED 09/n°106

Monsieur Pierre GLORIEUX
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

Monsieur le Directeur,

Je vous remercie pour l'envoi du rapport de comité de visite concernant l'unité « **UMR-S 561 Immunologie, génétique du diabète de type 1, génétique multifactorielle en endocrinologie pédiatrique** » rattachée à mon établissement.

L'Université a pris bonne note des remarques du comité de visite et veillera, en partenariat avec l'INSERM, à ce que les recommandations faites soient suivies d'effet.

Je vous prie de croire, Monsieur le Directeur, à l'expression de ma meilleure considération.

Le Président de l'Université

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Paris, March 20, 2009

We thank the AERES visiting committee for its appreciation of our project and for its kind comments and analysis of our scientific projects and production, within the general context of human disease and of mouse experiments.

Our answers to the specific questions and remarks of committee members are following the order indicated in the Review document.

1. *Team 2 needs to attract more young researchers to guarantee its future. The number of post-docs, and young researcher was in contrast limited for Team 2.*

Team 2 currently has 4 PhD students, Stéphanie Mehouas from Ecole Normale Supérieure, Virginie Marriot, Emmanuelle Motte, Gwendoline Albert and a PhD student, Delphine Fradin, who got an European grant for a post-doctoral stay at Johns Hopkins Epigenetics Center. Team 2 seniors are 2 Professors of Pediatrics, half-time researchers, 1 Directeur de Recherche and 1 Chargé de Recherche. We do not agree with the proposition of attracting more than 4 doctoral students, and 1 post-doc for the moment. We will carefully select among our students who will be proposed to become a future members of the team. It is likely that Delphine Fradin will attempt to find a INSERM or University position when back from her post-doc time (2010), and that Stephanie Mehouas will enter a research career with us after her PhD. We are happy with these perspectives, and do not plan to involve more young people for the time being, given our projects and critical mass of seniors.

2. *Technical help is not shared between researchers, such as the flow cytometry core facility.*

People. Team 1 organization of 6 technicians is « per researcher » as often in French labs: it is efficient and people appreciate the way it is, so that we see collectively no reason to modify it for the moment. Team 2 technicians are only 1 (Christine Dos Santos). As pointed out by several committee members to Pierre Bougnères, we will need to ask INSERM direction for a better balance between the Teams by hiring a full-time INSERM tech, thus allowing a better sharing of technical support.
Machines. With respect to the techniques, the comment about the FACS seems a bit unappropriate since the 3 teams who use the platform (Roberto Mallone, Christian Boitard, Agnès Lehuen from Team 1, and Caroline Silve from Team 2) did not understand the reason for the comment, while they use to share the FACS without any problem and good exchanges (maybe a minor negative problem raised by one of the technicians has inspired the comment?). To the best of my knowledge, Q-PCR, Light Cyclers, cell culture, etc are shared with a good spirit and efficacy.

3. *Absence of common seminars and shared information between the 2 Teams. There is limited evidence of strong interactions between the 2 Teams.*

It is always true that more intellectual exchanges help build good science. We have faced however specific limitations to this general incentive. Roberto Mallone, Caroline Silve, Agnès Linglart joined within only the

last 2 years, and are still striving to produce good science in their respective area of research. They head small groups. Life outside a large Institute requires everybody efforts to be competitive. A team working on the epigenomics of the GNAS locus in pseudohypoparathyroid infants composed of a Professor of pediatrics, a young technician to be trained, and a PhD student does not have much time to share seminars with a class I immunologist who is working 100% with her technician and PhD student on the dendritic cells dynamics in virally-induced immune phenomena. Only time and discussions will help build common projects, if they are to have a scientific foundation. Each little group has its specific meetings and seminars, and collaborations, as a step 1 unit of middle size. Given the friendship between the seniors, and their scientific motivation, I have little doubt that some will find common approaches of shared questions. What I foresee for example, and am working on personnally is :

1. Approach the epigenetic regulation of « autoimmune » gene expression and immune phenotypes in slected categories of circulating lymphocytes in Type 1 children (implicating Agnès Linglart, Roberto Mallone, Caroline Silve, Christian Boitard, Pierre Bougnères)
2. Explore the consequences of experimental modulation of methyl-diet in NOD mothers on thymic and beta-cell gene expression and diabetes phenotypes of their F1, F2, F3 offspring (Catherine LeStunff, Roberto Mallone, P.Bougnères)
3. Attract Team 1 in the Team 2 setting of a large type 1 diabetes cohort at the national level for the study of genetic-environmental predisposition to autoimmune diabetes (R.Mallone, C.Boitard, S.LeFur, P.Bougnères)

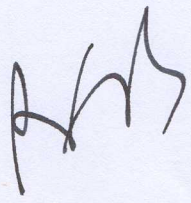
I am confident that the potential for joining forces on such approaches (or others) will emerge quietly in a near future.

4. *Improve the fluidity of information, possibly through regular meetings with staff representatives.*

We all agree that managing lab communication is needed. It will be developed to a better extent with a monthly « Conseil de laboratoire» headed by one of the Team leader alternatively allowing everybody to have a better view on the organization and prospects.

5. *Gain international collaborations and support.*

I think Team 1 has developped several good-level international projects (see the last publication of A.Lehuen as an example) as well as Caroline Silve and Agnès Linglart collaboration that the AERES committee's comment is mostly directed at Pierre Bougnères's group. It is 100% true that P.Bougnères team has had very little international collaborations and almost no engagements in european grants or consortia. Now that P.Bougnères has less duties and more time for enlarging its research approaches, he will do his best for developing more international collaborations.



Pierre Bougnères