Pathogenèse virale du diabète de type 0

Rapport Hcéres

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

Department for the evaluation of research units

AERES report the research unit:

Viral pathogenesis of type 1 diabetes

Under the supervision of the following institutions and research bodies:

Université Lille 2 – Droit et Santé

January 2014

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 Agnès LEHUEN, 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:	Viral pathogenesis of type 1 diabetes
Unit acronym:	
Label requested:	EA
Present no.:	EA 3610
Name of Director (2013-2014):	Mr Didier HOBER
Name of Project Leader (2015-2019):	Mr Didier HOBER

Expert committee members

Chair: Ms Agnès LEHUEN, Institut Cochin, Paris

Experts:

Ms Anne COOKE, Cambridge University, United Kingdom

Mr Gun FRISK, Uppsala University, Sweden

Mr Bruno POZZETTO, Université Jean Monnet, Saint-Etienne (representative of CNU)

Scientific delegate representing the AERES:

Mr Joost VAN MEERWIJK

Representatives of the unit's supervising institutions and bodies:

Mr Régis BORDET, Université Lille 2 – Droit et Santé

Mr Philippe DELANNOY (Doctoral School n°446 "Biology and Health")

1 • Introduction

History and geographical location of the unit

The laboratory "Viral Pathogenesis of Type 1 Diabetes" (EA 3610 Université Lille 2, directed by Mr Didier HOBER) is the renewal of the laboratory originally established by Mr Didier HOBER in 2002 and then renewed in 2006 and 2010. It is located on the site of the University hospital of Lille. This laboratory is strongly linked to the Virology Department of the hospital, CHRU Lille, headed by the unit's director since 2003.

Management team

This small unit is directed by Mr Didier HOBER.

AERES nomenclature

SVE1_LS6 Immunology, microbiology, virology, parasitology

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	6	5
N2: Permanent researchers from Institutions and similar positions	1	1
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	1
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	5	6
N6: Other contractual staff (without research duties)	3	2
TOTAL N1 to N6	**17**	**16**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit*		
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	5	5

2 • Overall assessment of the unit

The laboratory "Viral Pathogenesis of Type 1 Diabetes" is internationally recognized for its contributions to the analysis of the role of enterovirus, especially Coxsackieviruses (CVB), in the pathogenesis of type 1 diabetes (T1D). Participation in international networks has allowed the director to analyse the presence of anti-CVB antibodies in the blood of T1D patients. This expertise in the characterization of anti-CVB antibodies, rather unique world-wide, gives the team a leading position in the field. The publications resulting from this activity are very good for original articles and excellent for reviews/editorials. The experimental research concerned several aspects of CVB infection: analysis of anti-CVB antibodies in T1D patients, study of viral persistence that could promote the development of T1D through several mechanisms. In this regard the laboratory is analysing the potential role of enhancing anti-CVB antibodies in the persistence of viral infection and the development of T1D. However, its expertise in measuring antibodies should be strengthened by a better characterization of the molecular targets of the enhancing and neutralizing anti-CVB4 antibodies in the coming years. Overall, the research done in the laboratory during the last five year is qualified by the experts committee as very good for the aspects on virology and good for the link to T1D. It is important to stress that this team is one of the few virus laboratories in the world working on the role of viruses on T1D. The work is very good for a small team, in which all permanent researchers have clinical and teaching duties.

Strengths and opportunities related to the context:

- originality of the project;

- interactions within the FP7;

- international recognition on CVB and type 1 diabetes;

- enthusiasm of the whole team;

- interactions with developing countries;

- several industrial contracts, particularly for inactivation of virus.

Weaknesses and threats related to the context:

- lack of full time researchers;

- no interaction with structural biologists;

- no access to cell-sorter for infected cells (L2) to identify cells in PBMC;

- insufficient interactions with local clinicians in endocrinology and internal medicine for analysis of cohorts;

- lack of A2 facility (but should open in 2014);

- the experts committee feels that the main threat is the dispersion of the objectives.

Recommendations

The experts committee strongly recommends to set up priorities among the projects and particularly to focus on the antibody targets for VP4 and enhancing antibodies, the mechanism of virus persistence, and the cells involved in this persistence. Collaborations with structural biologists and clinical teams to bring cohort samples are also highly encouraged. The unit should also be more aspirational in the choice of their journals.

3 • Detailed assessments

Assessment of scientific quality and outputs

The laboratory "Viral Pathogenesis of Type 1 Diabetes" is internationally recognized for its contributions over many years to the analysis of the role of enterovirus, especially Coxsackieviruses (CVB), in the pathogenesis of type 1 diabetes. The director's important participation in international networks of the European FP6 and FP7 programs has allowed him to analyse the presence of anti-coxsackievirus antibodies in the blood of type 1 diabetic patients (mainly from Finland). This expertise in the characterization of anti-CVB antibodies, rather unique world-wide, gives the team a leading position in the field. The publications resulting from this activity are very good for original articles (J. Virol., Cell. Mol. Life Sci.) and excellent for reviews/editorial (Nat. Rev. Endocrinol., Rev. Med. Virol., British Medical Journal). There are two collaborative publications with the University of Tampere Finland and Virdiab consortium (FP6) EC in Diabetes (IF 8.2) and with the University of Exeter, United Kingdom and Pevnet consortium (FP7) in Diabetologia (IF 6.8).

The experimental research concerned several aspects of CVB infection: analysis of anti-CVB antibodies in T1D patients from a Finish cohort, study of viral persistence that could induce/promote the development of type 1 diabetes through several mechanisms such as chronic pancreatic inflammation, altered beta cell differentiation and lack of intrathymic T-cell tolerance-induction. In this regard the laboratory is analysing the potential role of enhancing anti-CVB antibodies in the persistence of viral infection and the development of diabetes. The analysis of these antibodies against CVB4 is performed by ELISA and by in vitro cell infection, which have been developed by the team. However, its expertise in measuring antibodies should be strengthened by a better characterization of the molecular targets of the enhancing and neutralizing anti-CVB4 antibodies in the coming years. Another aspect concerns the analysis of thyroid CVB infection in patients suffering for thyroid pathologies. In 2010, a microbiologist of the Faculty of Pharmacy joined the team with her group and she is particularly interested in the influence of the gut microbiome and human breast milk in the development of type 1 diabetes in NOD mice.

Overall, the research made in the laboratory during the last five year is qualified by the experts committee as very good for the aspects on virology and good for the link to type 1 diabetes. It is important to stress that this team is one of the few virus laboratories in the world working on the role of viruses on type 1 diabetes. The evaluation of the work (type and number of publications) is very good for a small team, in which all permanent researchers have other clinical and teaching duties. Perhaps the unit should be more aspirational in the choice of their journals.

Assessment of the unit's academic reputation and appeal

The laboratory's director is involved in European consortia (i.e. Pevnet FP7 and Virtex FUI programs). Although the laboratory is not coordinating these programs, participation in networks of such high level demonstrates the visibility and recognition of the team.

The laboratory's director has co-organized the "9ème Congrès Société Française de Microbiologie Lille 2013" and was invited to international meetings: Symposium Vidis EASD Rome 2010, Symposium Vidis EASD Stockholm 2011. He also gave seven invited lectures: Diamenord 2009, Société Française de Diabétologié 2010, Karolinska Institute Stockholm 2010, Institut Pasteur de Lille 2011, Symposium JDRF EASD Berlin 2012, Société Française de Microbiologie Lille 2013, and participated twice as opponent in juries of PhD defenses at the Karolinska Insitute and in Uppsala.

There are several Master and PhD students from foreign countries (Tunisia, Congo, Peru, Lebanon).

The development of unique assays to analyse enteroviruses by this laboratory opens up the potential for numerous collaborations.

The unit's academic reputation and appeal is qualified by the experts committee as very good.

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

The laboratory has developed methodologies for anti-CVB antibodies (anti-VP4 for ELISA and in vitro culture infection, and neutralizing antibodies for the viral neutralization). The unit has obtained several regional contracts with industrials: Contract Notivir Région/Feder (Pôle de compétitivité Up'tex), Contrat Rubinov Région/Feder (Pôle de compétitivité PNSL). These are recognized innovations with patents (one patent on ELISA for CVB is licensed) and several industrial collaborations (e.g. Cifre fellowship).

The unit's director is member of the European committee for standardization (inactivation of virus), expert in the committee Biocide ANSM, member of the Jury "Création d'Entreprises Innovantes" (2007-2013, Ministry of Research-Oséo), and of the evaluation committee ALIA and ALID (ANR): 2008-2013.

The experts committee particularly appreciated the efficacy of the unit's director in developing strong and regular links with industry due to his expertise in the study of enteroviruses.

The committee qualified the interaction of the unit with the social, economic and cultural environment as excellent.

Assessment of the unit's organisation and life

There are weekly laboratory meeting with all the members to discuss the data. All members of the unit seem enthusiastic about their projects. There is a good atmosphere and secure funding for the PhD students, the post-doctoral fellows, and the technicians/engineers. The experts committee recommends to encourage the organization of journal clubs (to discuss original articles) as well as participations to national/international meeting for the members of the team (permanent researchers, postdoctoral fellows and PhD students). There are very well defined procedures for laboratory experiments and particularly the ones performed with viruses (in L2 facilities). Interactions with other teams of the campus and in Lille (working on similar topics such as diabetes and virus) could be strengthened.

Assessment of the unit's involvement in training through research

Many of the permanent researchers participate in teaching. The unit's director is co-responsible for the Master 1 program in "Pathophysiology of infectious agents" at the Faculty of Medicine of Lille and responsible for a University Diploma (DU) of Virology (Diploma of Virology), encompassing a research module and research-training.

The laboratory is strongly involved in training Master and PhD students. Eight Masters and five PhD theses were defended during the last contract. Several Master and PhD students are from foreign countries; Congo, Tunisia, Peru and Lebanon. All PhD students have annual assessment by the PhD council and the Doctoral School. All the PhD students defend their PhD with several publications and at least one as a first author. This team is strongly involved in teaching and training

Assessment of the strategy and the five-year plan

The unit will need to define priorities. Considering the size of the group, there are too many aspects of the project to be able to work in depth on each of them. The unit should focus on some specific aspects:

1) to better define the molecular interactions between the antibodies and VP4 (characterization of the epitopes involved), collaborations with structural biologists would be important to better analyse how VP4 protein could be exposed at the surface of the virus to allow its recognition by the antibodies;

2) to further characterize the neutralizing and enhancing antibodies: molecular targets, epitopes, isotypes, affinity. Analysing mutant viruses with modified VP4 would be an interesting strategy for determining whether there is a link between the specificities of the antibodies and the persistence;

3) to determine the cell types that are infected in the blood of type 1 diabetic patients and that could be implicated in the persistence of the CVB4 virus.

The set-up of new collaborations should be considered to address these important aspects of the project.

While the microbiology aspect is very interesting, there might be some concern about international competition. Competitive edge would be achieved by a close collaboration effort to identify the interactions between some bacteria of the microbiota and the CVB.

4 • Conduct of the visit

Visit date:

Start: Tuesday, January 21th 2014 at 09.00 am

End: Tuesday, January 21th 2014 at 04.00 pm

Visit site:

Institution: Université Lille 2, CHRU Lille

Address: Institut Hippocrate CHRU Lille - 152 rue du Dr Yersin - 59120 Loos-lez-Lille

Conduct or programme of visit:

09.00 to 09.30 am — Closed door meeting: expert committee members and AERES scientific delegate (DS)

09.30 to 10.30 am — Presentation of past activity and projects of the unit by Mr Didier HOBER (director)

10.30 to 11.00 am — Coffee break

11.00 to 11.45 am — Parallel meetings of expert committee members and DS with:

- Engineers, technicians and administrative assistants;
- PhD students and postdoctoral fellows;
- researchers with permanent position (except the unit's director).

11.45 to 12.15 pm — Meeting with representatives of the Université Lille:

- Mr Régis BORDET, Université Lille 2 ;
- Mr Frédéric GOTTRAND, Lille University Hospital;
- Ms Monique CAPRON, Université Lille 2

12.15 to 12.30 pm — Meeting with the representative of the Doctoral School:

- Mr Philippe DELANNOY, ED n°446 "Biology and Health".

12.30 to 01.30 pm — Lunch buffet

01.30 to 02.00 pm — Closed door meeting of the experts committee and DS with the unit's director

02.00 to 04.00 pm — Closed door meeting of the experts committee and DS

5 • Supervising bodie's general comments

Université Lille 2
Droit et Santé

Service de la Recherche, de la Valorisation
et de l'Information Scientifique (SeRVIS)
Affaire suivie par Christophe BOUTILLON
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Le Président de l'Université

à

Monsieur le Professeur Pierre GLAUDES
Directeur de la Section des unités de recherche
Agence d'Evaluation de la Recherche et de l'Enseignement Supérieur (AERES)
20 rue Vivienne
75002 PARIS

Lille, le 28 mars 2014

V/Réf. : E2015-EV-0593560Z-S2PUR150007568-005872-RT

Objet : Observations de portée générale sur le rapport d'évaluation de l'unité *Viral pathogenesis of type 1 diabetes*

Monsieur le Directeur,

Considérant le rapport que vous m'avez récemment transmis, je vous remercie au nom de l'Université Lille 2 et en particulier du directeur et des membres de l'unité *Viral pathogenesis of type 1 diabetes,* pour la qualité de l'évaluation effectuée le 21 janvier 2014 par votre comité d'experts.

Les appréciations et recommandations formulées seront soigneusement prises en considération et discutées avec le directeur de l'unité dans le cadre de la structuration de notre recherche pour le prochain plan quinquennal (2015-2019).

Vous trouverez ci-dessous les observations de portée générale sur le rapport d'évaluation de l'AERES, émises par le Directeur de l'unité *Viral pathogenesis of type 1 diabetes.*

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

Pr. Xavier VANDENDRIESSCHE

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March 24, 2014

To Aeres committee members

The members of EA3610 thank the committee members for the visit and the evaluation.

The members of the Unit are glad to realize that their efforts are acknowledged. The overall assessment of the unit indicates that the laboratory "Viral Pathogenesis of Type 1 Diabetes" is internationally recognized for its contribution to the analysis of the role of enterovirus, especially coxsackievirus B (CVB), in the pathogenesis of type 1 diabetes (T1D). The report indicates that the research done in the laboratory during the last five years is very good for the aspects on virology and good for the link to type 1 diabetes. The committee mentioned in the report that the team is one of the few virus laboratories in the world working on the role of viruses on T1D, and that the work is very good for a small team in which all permanent researchers have clinical and teaching duties.

Furthermore the committee mentioned that the unit's academic reputation and appeal is very good, and that the interaction of the unit with the social, economic and cultural environment is excellent. It has been noticed by the expert committee members that the team is strongly involved in teaching and training, that all the members of the unit seem enthusiastic about their projects and that there is a good atmosphere and very well defined procedures for laboratory experiments.

The members of the Unit thank the expert committee members for their criticisms displaying a few weaknesses and for their recommendations. Studies addressing issues raised by the experts in the report are in progress and will be further developed in the future.

Pr Didier Hober

Le Président de l'Université

Xavier VANDENDRIESSCHE