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

Department for the evaluation of research units

AERES report on unit:

Translational Research in Diabetes

RTD

Under the supervision of the following institutions and research bodies:

Université Lille 2 – Droit et Santé

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,

- Mr. Hubert VIDAL, 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 experts committee,the composition of which is specified below.

The assessment contained herein are the expression of independent and collegial deliberation of the committee.

Unit name:	Translational Research in Diabetes
Unit acronym:	RTD
Label requested:	UMR_S
Present no.:	UMR_S859
Name of Director (2013-2014):	Mr François PATTOU
Name of Project Leader (2015-2019):	Mr François PATTOU

Expert committee members

Chair:

Mr Hubert VIDAL, University of Lyon 1

Experts:

Mr Michelangelo FOTI, Genova University, Suisse

Mr Jean-Christophe JONAS, Catholic University of Louvain, Belgique

Mr Etienne LARGER, Paris Descartes University (représentative of CNU)

Ms Agnès LEHUEN, Paris Descartes University (représentative of CSS INSERM)

Scientific delegate representing the AERES:

Mr Jean GIRARD

Representative(s) of the unit's supervising institutions and bodies:

Mr Régis BORDET, University of Lille 2

Mr Samir OULD ALI, Inserm

Mr Bernard SABLONNIERES (Head, doctoral school Biology and Health n°446)

1 • Introduction

History and geographical location of the unit

The Research Unit "Biotherapies of Diabetes" is a Bipartite unit of the Université Lille 2 - INSERM. After being a University team (EA 1044), the unit was labeled by INSERM as ERIT-M in 2000, before becoming UNIT-M in 2005 and UMR 859 in 2009. Since 2011, the UMR 859 is also one of the three components of the Research Federation EGID, that got a LABEX under the Investment for the Future Programme.

The Unit is located on the campus of the University Hospital of Lille, within the Pole Research of the Faculty of Medicine (3rd floor), where it occupies premises of about 1100 m2.

Management team

The direction committee of the UMR includes the two team managers and the head of the production platform of pancreatic islets, assisted by the administrative officer and two members of the UMR.

AERES nomenclature SVE1_LS4

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		1
N3: Other permanent staff (without research duties)	8	12
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	4	6
N6: Other contractual staff (without research duties)	17	13
TOTAL N1 to N6	**37**	**40**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	8	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit*	4	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	6	10

2 • Overall assessment of the interdisciplinary unit

The laboratory "Translational Research in Diabetes" is a continuation of the laboratory "Biotherapy of diabetes" (headed by Mr François PATTOU), established in January 2010 and strengthened by the arrival in 2012 of the "Experimental Diabetes" team, led by Amar Abderrahmani, who holds an ANR Chair of Excellence. The laboratory is internationally recognized for its contribution to the development and validation of islet transplantation in patients with type 1 diabetes. Publications are globally of very good level (with some excellent recent productions : NEJM, Gastroenterology, and Nature and J Clin Invest in collaboration). The overall project of the Unit aims to improve the care of diabetic patients with a clear objective of clinical translation, based on experimental research. Strengthening complementarity and interaction between these two components of the laboratory will undoubtedly allow the realisation of the projects. The research Unit is in a very favorable environment with the recent creation of the EGID federation.

Strengths and opportunities related to the context

Well recognized laboratory with world class expertise clearly identified in the field of islet transplantation.

Charisma and strong reputation of the director.

Recent arrival of a new team focused on more fundamental research on beta cell survival.

Creation of the Laboratory of Excellence EGID gathering 3 laboratories in Lille and construction of a building to allow development in the same geographic site.

Strong support from local institutions.

Weaknesses and threats related to the context

Laboratory mainly based on university-professors (mainly clinicians) who can not devote full-time to research.

Risk of dispersion if the interactions between the "historical" members of the laboratory and the newly arrived team are not put more into perspective, with common goals.

Recommendations

Recruitment of full-time researchers and international postdocs is important to stabilize the activity of the laboratory.

Given the current strengths, particular attention should be paid to better ensure consistency between the various projects proposed for the next five-year to avoid the risk of dispersion.

3 • Detailed assessments

Assessment of scientific quality and outputs

The Laboratory " Translational Research in Diabetes " (UMR 856 INSERM-University - CHU Lille Lille 2 , directed by Mr François PATTOU) is the direct continuation of the Laboratory "Biotherapie du Diabetes" (Director Mr François PATTOU), established in January 2010 and strengthened by the arrival in 2011 of the team "Diabète Experimental", led by A. Abderrahmani who holds a Chair of Excellence ANR (2010-2014) and is appointed Professor at the Université Lille 2.

The laboratory is internationally recognized for its long-term contributions to the development and validation of pancreatic islet transplantation in type 1 diabetic patients (Mr François PATTOU, MC VANTYGHEM). An important commitment from the Hospital allowed the setting of a "cell therapy laboratory" for islet preparation with international standards (J. KERR-CONTE). This expertise, rather unique in France, gives to the team of Mr François PATTOU a leader position in the field. The publications resulting from this activity are excellent (NEJM, JCEM, Gastroenterology, Diabetes Care, Am J Transplant).

In the context of bariatric surgery (also calleds "metabolic " surgery), used as therapeutic approach in type 2 diabetes, the team of Mr François PATTOU is developing an extremely original tissue bank (ABOS collection with biopsies of liver, adipose tissue and muscle) with samples obtained before and after surgery as well as at 1, 5 and 10 years of follow-up. Over 900 patients (1000 planned) have been collected so far. The access of this tissue bank to industrial, academic and international partners allowed important collaborations and co-publications in highly visible journals (Nature, J Clin Invest). The use of the bank in internal research programs should be develop in the coming years.

The main experimental research lines are: the study of beta cell survival using the biological material that cannot be used for graft (J. KERR-CONTE) and the study of molecular mechanisms controlling apoptosis in models of cultured beta cells (A. ABDERRAHMANI). Significant results were 1) the demonstration of the possibility of proliferation of adult human beta cells in a model of islet transplantation under the renal capsule in mice (Diabetologia and 2) the characterization of signalling pathways (ICER, JNK3) involved in the protection of beta cells against "diabetogenic" stress (Diabetes, Diabetologia).

The experimental part of the unit was strengthened by the recent arrival of team 2, which aims at addressing the molecular mechanisms involved in the survival of beta cells. This arrival also fulfills the requirement made by AERES in 2009 to further develop the experimental component of the laboratory. Attention still needs to be paid to the integration of this new team in the unit, especially to put it in coherence with the global research objective of the laboratory.

Overall, the research output of the laboratory during the last 5 years is qualified as excellent by the committee. The importance of the clinical research and the transfer to clinical practice has provided an international recognition of the group of Mr François PATTOU. The arrival of a more experimental component is appreciated. The type and number of publications, industrial contracts, patents, invitations is at the level that can be expected from a team of this size, working at the front of the research in the field of diabetes .

Assessment of the unit's academic reputation and appeal

The laboratory is a component of the EGID research Federation, granted Laboratory of Excellence in 2012, which demonstrates the importance and the quality of the research in the field of diabetes in Lille.

One of the team is involved in several European networks supported in the framework of the FP7. Although the laboratory is not coordinating these programs, participation in networks of high levels demonstrates the visibility and recognition of the team.

A. Abderrahmani got a (CNRS- Université Lille). The arrival from Lausanne of a recently appointed full-time professor position at the Université Lille with a "Chair of Excellence" from ANR clearly shows the attractiveness and recognition of the laboratory and of the EGID Federation.

Access to human pancreatic islets of high quality and the ABOS collection give a very strong appeal to the laboratory, opening the possibility to numerous collaborations. The establishment of a "Summer course" in diabetology with EGID should also allow greater attractiveness of international students and postdocs in the coming years.

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

The laboratory has developed methodologies and innovative approaches for islet transplantation in type 1 diabetic patients. These include the upstream aspects (preparation of islets from donor pancreas), the transplant procedures (optimization of preservation solutions, evaluation of immunosuppressive procedures) as well as the surgery by itself (search for alternative graft sites, such as muscle). These are recognized innovations with patents and industrial collaborations, leading among others to the development of an integrated culture system for human islets (called PRISM, in partnership with the MacoPharma company).

Team 2 is also interacting with industrial partners within the scope of his project on the use of peptides to modulate signaling pathways involved in survival/apoptosis of pancreatic beta cells. These approaches would benefit from being developed in a more concerted manner with the other projects of the research Unit.

The implementation and coordination by the Unit of the “cell therapy laboratory”, highly functional and certified for the preparation of biological materials for therapeutic, must also be emphasized in the socio -economic impact of the laboratory. The quality process and ISO certification of this structure should serve as a basis for improving the procedures and operation of the rest of the unit.

Assessment of the unit's organisation and life

The laboratory is rather small in size and based on 8 university-teachers, including 6 clinicians, some students and a significant number of technical staff (most of them with a CDD). A significant effort was made in recent years with the university and the hospital to provide long-term support to several contracts under the form of CDI, and a position for a technician (university) will be open in 2014. This organization was operational in the context of a clinical research laboratory. With the development of more mechanistic research axes, it will be important to better define a policy aiming at recruiting full-time researchers.

Organization and life of the laboratory (seminars, meetings, management) seems operational given the size and location of the teams in the vicinity of the Surgery departement and the Laboratory of Cellular Therapy. A specific problem in the organization of the gestion/administration has been corrected recently with the support of EGID and INSERM. The current premises are compatible with laboratory activity and the construction of new laboratories dedicated to the EGID federation will open opportunities for growth if necessary. It will be important to accelerate the dessimination of a Quality Assurance Procedure to the whole unit. The constraint of night (or week-end) work for some of the staff (for the preparation of islets according to the arrival of the pancreas) is generally well managed (with the CHU), but a better organization of work outside office hours for other staff of the Unit is required (statement for isolated workers, risk assessment in DUER, implementation of individual sheets of exposure for all stafff).

Assessment of the unit's involvement in training through research

The laboratory is rather small in size (6 HDR). The doctoral training activity remains limited, but of excellent quality with training doctors for research, allowing them to integrate a university hospital career (2 recruited over the last 4 years). The creation of a new teaching in the Master 2R and the organization with EGID, a "Summer Course" of diabetes have been noticed. No difficulty with the Doctoral School has been noted during the discussion with the director.

Assessment of the strategy and the five-year plan

The research program of the laboratory, in the continuity of its past activities, is perfectly logical and appropriate. The integration of a more mechanistic research line on the survival of beta cells is certainly a very positive point for better positioning the unit among the leading research laboratories in Europe. It will be important, however, to ensure consistency and synergies between this new team and the experimental approaches of the laboratory which aims at improving the therapy of diabetes.

The involvement of the laboratory in EGID is a major issue , allowing functional and very high level intractions with the laboratories of B. STAELS and Ph. FROGUEL. Theses collaborations must be maintained and expanded. Participation in European networks, already effective, is to continue through H2020. However, attention must be paid to a real initiator and coordinator of scientific programs likely to attract postdocs and researchers.

Analysis of strengths and weaknesses made by the laboratory is highly relevant and clearly shows the very important opportunities in Lille at the moment (ELabEx EGID, regional dynamics and strong support from local institutions, importance of the topic, tools and original apporches).

conclusion

- ***Strengths and Opportunities :***

Laboratory with well recognized international expertise clearly identified in the field of islet transplantation. Charismatic director with strong reputation. More fundamental ongoing research lines on beta cell survival with the arrival of the new team 2. Creation of the Laboratory of Excellence EGID gathering 3 laboratories, and construction of a building to allow its development in the same geographic area. Strong support from local institutions (university, hospital and INSERM)

- ***Weaknesses and Threats:***

Laboratory based solely on university professors (mainly clinicians) who can devote only part of their time to research. There is a risk of dispersion if the interactions between the "historical" members of the laboratory and the newly arrived team are not put in a better perspective with a common goal and real synergy.

- ***Recommendations:***

The recruitment in the near future of full-time researchers and international postdocs is important to stabilize the laboratory. Given the current strengths, particular attention should be paid to better ensure consistency between the various projects proposed for the next five-years and to avoid the risk of dispersion.

4 ● Theme-by-theme analysis

Team 1 : Biothérapie du Diabète

Name of team leader: Mr François PATTOU

Workforce

Team workforce	Number as at 30/06/2013[1]	Number as at 01/01/2015[2]
N1: Permanent professors and similar positions	7	7
N2: Permanent EPST or EPIC researchers and similar positions		1
N3: Other permanent staff (without research duties)	8	11
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	3
N6: Other contractual staff (without research duties)	13	9
TOTAL N1 to N6	**30**	**31**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	5	8

• Detailed assessments

Assessment of scientific quality and outputs

The research projects conducted by team 1 are highly original and have led to several landmark studies in the field. This is particularly obvious for the clinical studies investigating new sites of implantation (e.g. muscles) for islets grafts in type 1 diabetic patients, as well as those investigating the effects of bariatric surgery on patients with type 2 diabetes.

Overall, the novelty and quality of the work performed by this team and its scientific productivity is excellent with some clear outstanding contributions (NEJM, Gastroenterology,…). Some of their contributions are pioneering studies with trend-setting implications and even practice-changing impact for diabetic patients. The fact that this team is routinely and consistently publishing in relevant journals of this speciality represents strong evidence of the innovative and importance of their work, carried-out despite many of the researchers having important clinical and administrative responsibilities.

Together, researchers of team 1 have produced 92 publications including 50 original articles/reviews as first or last authors. The productivity is however variable among the PIs of the team. A significant number of co-authored publications are collaborations with reputed French or international research groups for whom the laboratory has provided human materials. Although this collaborative research is not a direct contribution of the team, providing other research groups with exclusive and high quality human material (in particular Langerhans islets) is a very important and crucial contribution to the scientific community for the advancement of the research on diabetes. In this regard, the current constitution of another biobank including tissues coming from obese/diabetic patients well characterized at the clinical level (cohort ABOS), will be also of a very high interest not only for this team but also for the whole scientific community working on metabolic disorders associated with obesity.

Finally, the arrival of a new team (team 2) with clear and demonstrated expertise in the cell biology of beta cells should nicely complement the clinical work already on-going and further promote the translational research aspects characterizing this laboratory.

Assessment of the team's academic reputation and appeal

Team 1 has undoubtedly acquired over the last years, a recognized international reputation as a leading group in pancreatic islet allo-transplantation. Their capacity to provide human islets of quality to other national/international teams has further established and reinforced their scientific reputation of excellence in this field of research. The completion of the ABOS cohort is also likely to further promote their international visibility and to expand their network of collaborators worldwide.

The team has received several grants from local, national and international agencies. In addition, the team is involved in several European and international consortia (FP7 Beta cell therapy, IMI direct, European consortium for islet transplantation, Collaborative Islet transplant registry). The capacity of the team to raise funds dedicated to its research and clinical trials not only reflect the dynamism of the group leader but also their national/international recognition by funding agencies and their peers. Finally, this team is part of the EGID (European Genomic Institute for Diabetes) which was recently accredited LABEX in 2012.

The work of this team is very much seen as trend-setting with clear potential benefits for patient populations. The numerous invitations to present their work at national and international meetings confirm the high visibility and recognition of the team members as well as their capacity to provide innovative research in the field of diabetes management.

In summary, team 1 benefits of an excellent national and international visibility, appeal and reputation.

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

Team 1 has performed very well in producing research that can be translated into clinical applications. The work of the team has resulted in particular into two filed patents related to the isolation and preservation of human Langerhans islets, as well as two industrial contracts (Macopharma for the development of a performing system to culture human Langerhans islets, PRISM; and Cousin Biotech for the development of a medical device used in mini-invasive treatment of diabetes).

The expertise and innovative therapies developed by this group have led also to several reports in the lay press and on national radio and television. The team obtained also financial support from private companies in particular for the constitution of the ABOS biobank.

Since obesity and diabetes have reached pandemic proportions worldwide and have become a major problem of public health, the socio-economic impact of the research and clinical trials performed by this team is likely to become very important in the proximal future.

Overall, interaction with social, economic and cultural environment is excellent.

Assessment of the team's organisation and life

The Team appears to be well organized into coherent subgroups and managed effectively despite having a varied composition made up of clinicians, university professors, trainees and a technical platform dedicated to the isolation and culture of Langerhans islets for allo-transplantation. In this context, the team leader demonstrates high leadership skills and exerts a clear positive influence, not only on the laboratory atmosphere but also in terms of guiding and coordinating effectively the work.

This is highly valued in particular by the postdocs and PhD students. Team members meet on a regular basis to share results and participate to weekly meetings. There are no apparent interpersonal conflicts within the members of this team. One major concern of the leader is the urgent need for additional help with overwhelming administrative tasks in particular regarding the management of international/European grants and biobanks.

One can regret however that the staff of the technical platform isolating and evaluating the quality of human islet for allo-transplantation is not more deeply involved in basic/translational scientific projects. As well, whether efforts are promoted to train tomorrow's scientists and clinicians to ensure continuity of the research activity is unclear. The recruitment of full-time researchers should be considered to stabilize the team for the future.

Assessment of the team's involvement in training through research

A number of Ph.D students and postdocs are, or have been, associated with this team, few of which are not French nationals. Since 2006, 3 Ph.D thesis were awarded and 2 PHD students are currently trained. The postdocs and Ph.D students who graduated published at least a first-authored publication in journals of their specialities. The Team appears also sufficiently funded to allow trainees to travel to meetings when and where appropriate. Some of the projects in which postdocs or Ph.D student are involved are at high risk/high reward but apparently with no clear alternatives if unfruitful. It seems that the time the clinicians can dedicate to basic/translational research may to not be always adequate and sufficient to complete the rather ambitious team’s projects. This could also have impact on the training of students. Stabilisation of positions within the team for postdocs/Ph.D students should be more clearly defined as a strategy for the future.

Finally, members of the team 1 are contributing teaching duties in 3 different master programs from University of Lille 2, Paris Sud and Créteil.

Assessment of the strategy and the five-year plan

The five-year strategic plan of team 1 is centered on three different axis coherent with the different expertise of the senior clinicians/scientists. These include principally clinical studies but also some aspects of fundamental research derived from the clinical activity of team 1. The plan is well prepared and thought out to build upon the recent advances obtained by the team, as well as the availability of human islets and of a biobank of tissues from the ABOS cohorts of patients under construction. The plan includes several specific and highly innovative projects, which should ensure that the Team remains a leading authority in this area gaining concomitantly further national and international recognition.

These axis focus in particular on the following themes:

1. The improvement of the isolation procedure and quality of human islets for allo-transplantation and basic research. The study of islets biology using mouse models, in particular the impact of obesity on islet dysfunctions. For these fundamental aspects, team 1 plans to tightly collaborate with team 2, in particular by providing team 2 with human material of quality.

2. Various clinical trials and follow up of islets-transplanted patients. The clinical evaluation of alternative sites of implantation for islets allo-grafts and the development of mini-pig animal models of islets transplantation.

3. The analysis of the efficiency of metabolic surgery (gastric bypass, GBP) for the treatment of type 2 diabetic patients, in particular the retrospective analysis of the ABOS cohort. The development of new surgical methods for GBP and alternative non-invasive methods to mimic the GBP using a mini-pig animal model.

In addition to the research described above, team 1 plans also to develop other projects complementary to their research to open new perspectives for the future. In particular, they envisage i) to start characterizing iPS cells from patients of the ABOS cohort for therapeutic purposes, ii) to develop a mini-pig animal model to investigate obesity-associated metabolic diseases, iii) to perform clinical studies aiming at understanding factors promoting diabetes in stress conditions, and iv) to investigate in a multi-disciplinary approach the impact of habitation architecture on the alimentary behaviour (ABOS cohort).

Although these projects in their whole are coherent and complementary, they might be however a bit over-ambitious for the human resources currently available. In this regard, more detailed milestones and priorities on the developments of all these projects should be established. Also, most of the projects described are clearly clinical prospective or retrospective studies. More basic and translational aspects should be developed in the future through close interactions with the team 2 working on the Langerhans islet biology. In this respect, it is evident that team 1 will greatly help team 2 by providing human material of quality for their studies, however how team 1 will benefit from the work of team 2 is still quite unclear. Finally the development of the mini-pig animal model to investigate new surgical/nonsurgical methods for GBP and obesity-associated metabolic disease should be a priority to support the clinical activity of team 1 with more fundamental/translational research on type 2 diabetes also.

Conclusion

- ***Strengths and opportunities:***

Strong leadership.

Important questions with real potential translational benefits. Projects are focusing on relevant public health priorities.

Innovative and competitive clinical research.

Very good track record.

Good prospects for continued and increased national and international funding.

Good prospects of strengthening industry links.

Strong position to strengthen national and international collaborations in particular by providing high and reliable quality human materials.

Excellent opportunities for interactions within team 2.

- ***Weaknesses and threats:***

The limited size of the team compared with the large number of proposed projects.

The absence of full-time researchers and no well-established or apparent recruitment strategy of the next generation of leading researchers/clinicians.

Overwhelming administrative responsibilities.

Some of the research topics of postdocs/PhD students are at high risk.

Currently no translational research on type 2 diabetes to support clinical activities in metabolic surgery (GBP).

The development of new know-hows (e.g. iPS cells differentiation) is extremely time- and resources-consuming.

- ***Recommendations:***

The team would undoubtedly benefit from:

- Developing more efforts to attract foreign clinicians, students and scientists,

- Recruiting basic scientist working on T2D to further develop the mini-pig model of metabolic diseases (in addition to team 2 focusing on islets biology),

- Improving the commitment of scientist/technicians of the “Plateforme de Biothérapie” in basic research,

- Defining and allocating more carefully priorities and manpower for each axis of research,

- Continuing its excellent work!

4 • Team by team analysis

Team 2 : Diabète experimental

Name of team leader: Mr Amar ABDERRAHMANI

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		
N3: Other permanent staff (without research duties)		1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	3
N6: Other contractual staff (without research duties)	4	4
TOTAL N1 to N6	**7**	**9**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	2

Detailed assessments

Assessment of scientific quality and outputs

The research program of team 2 is centered on the understanding of the cause of beta-cell dysfunction/apoptosis in the context of type 2 diabetes, with specific focus on deregulation of general transcription factors (ICER) and on the roles of jun kinase (JNK) isoforms. This research gradually evolved from characterization of the mechanism of control of JNK isoforms and their deregulation by metabolic stress to attempts to find ways to interfere with these processes in order to improve beta-cell survival under diabetic conditions. This line of research has recently benefited from new access of team 2 to human islets through its interactions with team1. The recent installation in Lille does not yet result in visible outputs.

The scientific output of this team over the last 5 years is considered as very good taking into consideration the small size of the team and the fact that the production inevitably suffered from the move from Lausanne to Lille in 2011/2012. The team leader published 5 papers as last author in very good journals in the field (N Engl J Med, Gastroenterol, J Hepatol, Diabetes, Diabetologia, J Clin Endocrinol Metab), and contributed to 15 papers in the like. He did not, however, publish his results in general audience journals, which would bring more visibility to his work. His work is regularly cited by his pairs. The yearly number of citations increased from ~80 in 2008 to ~130 in the last few years. He was not invited as a speaker in international conferences, but the work of his team has regularly been accepted for communications in such meetings.

Assessment of the team's academic reputation and appeal

The team was created in the frame the EGID consortium in Lille (recognized Labex in 2012). The complementarity of this team with the activities of Prof. Mr François PATTOU laboratory logically supports their association in a single research Unit. Team 2 leader obtained an important ANR grant ("Chaire d'excellence" from université de Lille) to facilitate his installation in Lille. However, this grant is ending in a near future and the capacity of team 2 to attract PhD and postdocs and to develop its research plan will now depend on the ability to raise funds in the coming year.

Prof ABDERRAHMANI is editor for Plos One, a well-known Open Access journal covering all aspects of life sciences.

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

Because of the very recent installation of this group in Lille, the committee considered that it was not possible to correctly evaluate this item.

Assessment of the team's organisation and life

The global organization of team 2 seems adequate with respect to the size of the group and the type of research conducted. Two permanent positions (CDI) for technical staff have been allocated to the team by the research Unit and by EGID. Resources are accessible locally or through collaboration with team 1 and other members of the EGID consortium. Although a specific "welcome grant" form EGID was allocated to help the installation of the team, its ability to survive will depend on its capacity to raise new grants after the completion of the current ANR support. It should be noted, however, that this evaluation is considered premature in view of the fact that team 2 was created only recently.

Assessment of the unit's involvement in training through research

The involvement of team 2 to training through research is judged adequate based on interview of PhD and postdoc fellows from the lab and from the history of the team leader before his move to Lille.

Team 2 leader has created a new UE for the Master recherche Biologie-Santé and a new international summer research school starting from July 2014. Again, team 2 is too young to assess this point correctly.

Assessment of the strategy and the five-year plan

In the continuity of the work done during the past years, the research program of team 2 is centred on the understanding of the cause of beta-cell dysfunction/apoptosis, with a specific focus on the roles of the JNK isoforms. The proposed project comprises careful dissection of the mechanism of control of JNK3 by IB1 (a scaffold protein highly expressed in beta-cells) and upstream kinases such as DLK1 (also highly expressed in beta-cells). The objective is to understand whether a down-regulation of this pathway by metabolic stress in patients with T2D contributes to beta-cell demise. A complementary aim is to develop pharmacological approach to improve beta-cell survival by using peptides that mimic the beneficial effect of DLK1 and IB1-mediated activation of JNK3. The work will be performed initially in cell lines, but this research will strongly benefit from the access of team 2 to human islets through its interactions with team1. However, the molecular toolkit to study this pathway in human cells is incomplete and needs to be developed.

Although this project is original and could lead to new developments to fight T2D, a solid proof of concept of the importance of the DLK1-IB1-JNK3 pathway to beta-cell survival in the context of metabolic stress is needed. Only few preliminary (yet encouraging) results about the effect of JNK3 manipulation in vivo (transgenic mice) were available. Team 2 is therefore encouraged to further build on this type of study before going for a peptide strategy to interact with the pathway. This pharmacological approach may also not be the best, as peptides are not easily delivered at the right site of action. An alternative approach might be developed with non-academic partners when the target will be further validated in human islets. There are also some questions about the feasibility of this approach. Nevertheless, the committee thinks that it is worth giving the time to team 2 to test this hypothesis thoroughly. They should however try to develop this project in closer integration with team 1, with a global objective of the laboratory to improve the success rate of islet transplantation.

Conclusion

- ***Strengths and opportunities:***

The research program of team 2 is well focused, original and has the potential to lead to better understanding of protective mechanisms of beta cell survival, which should ultimately be important for the improvement in the success rate of islet transplantation in T1D and for the development of new treatment for T2D. The easy access to human islets and to ABOS collection, thanks to its interactions with team 1, should provide an advantage to team 2 in comparison with other research groups in the field.

- ***Weaknesses and threats:***

Attention should be paid to the stability of the group in the medium/long term. Regarding the project, it relies on detailed analyses of one pathway that will be targeted by a single risky pharmacological approach based on inhibitory peptides. No alternative program is proposed.

- ***Recommendations:***

The main recommendation of the committee is to further develop the interaction with team 1 in order to validate the role and importance of the JNK3 pathway in human islet with the aim of improving beta cell survival and function in the context of T1D (e.g. islet transplantation) and T2D. The group is still fragile and should be rapidly consolidated to ensure the sustainability of the proposed team.

5 • Déroulement de la visite

Date de la visite

Début : 2013 december the 9th, at 10h00

Fin : 2013 december the 9th, at 16h00

Lieu de la visite : Faculté de Médecine - Département Hospitalo-Universitaire de Recherche Expérimentale (DHURE), Université Lille2

Institution : Université Lille2 - Droit et Santé

Adresse (n° voie ville) : 1 Place de Verdun, 59045 Lille Cedex

Déroulement ou programme de visite :

09h30 - 09h45	Accueil des participants (Salle du conseil Rdc)
09h45 - 10h00	Réunion à huis-clos / Comité de visite + Délégué Scientifique de l'agence
10h00 - 10h30	Présentation générale et bilan du contrat en cours
10h30 - 10h45	Discussion
10h45 - 12h15	Projets scientifiques -Equipe 1 / Discussion -Equipe 2 / Discussion
12h15 - 12h30	Discussion générale
12h30 - 13h30	Repas et discussion avec les chefs d'équipe
13h30 - 14h00	Réunion avec tutelles et ED / Comité de visite
14h00 - 15h00	Rencontre doctorants / post-doctorants et Rencontre ITA
15h00 - 16h00	Délibération à huis-clos / Comité de visite

6 • Supervising bodies' 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
Directeur du SeRVIS
christophe.boutillon@univ-lille2.fr / 03.20.96.52.16

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 26 février 2014

V/Réf. : E2015-EV-0593560Z-S2PUR150008839-006967-RT

Objet : Observations de portée générale sur le rapport d'évaluation de l'unité *Translational Research in Diabetes (RTD).*

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 *Translational Research in Diabetes,* pour la qualité de l'évaluation effectuée le 9 décembre 2013 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 *Translational Research in Diabetes.*

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

Pr. Xavier VANDENDRIESSCHE

UMR 859 - Biothérapies du diabète

(INSERM / Université de Lille 2 / CHRU de Lille)

Lille February 25th

First, we would like, on behalf of all the members of our research unit, to express our gratitude to the president and the members of the Aeres committee for their time and the efforts put into this reviewing process as well as during their visit of our laboratory in Lille.

The detailed Aeres report was disseminated to all members of our research unit and discussed in depth during a specific unit council. The global analysis of the committee was greatly appreciated. We were indeed pleased to note the strengths of our project and its favorable environment (EGID) underlined in the report. More specifically, the arrival of a new team, focused on more fondamental research, was well received by the committee.

On the other hand, we paid the greatest attention to the sound suggestions and specific recommendations made by the committee, and will address each of them carefully in the coming year. We would also like to comment below some specific issues raised in the report, and to communicate to the committee complementary informations that could not be sufficiently detailed during the visit, or which were not yet available at that time.

Specific comments / Research unit

1. Overwhelming administrative responsabilities

This point already identified by our team and clearly underlined in the report is actively addressed. Indeed, since the visit, a full time secretary (Mrs Corrine Courcol) was appointed by Inserm to our team. Arrived in February, she is now assisting the director and the lab manager in the administration of our research unit.

Moreover, a 5 year contrat d'interface was confirmed in January by Inserm to the unit director. The recruitment of a personal assistant is envisioned for securing more time to research activities by optimizing the time devoted to administration.

2. Organisation and life of the unit

Since the visit, the policy for working outside office hours is being reorganized with the Direction des ressources humaines du CHRU. This point will be fully clarified before the end of 2014. Since the visit, safety measures for isolated workers have also been formalized.

Regarding quality assurance, beside the implementation of GMP for islet production activity which will be soon required by the European regulation, we will progressively

disseminate the quality assurance programme to the rest of the unit, under the coordination of Rimed Ezzouaoui. This policy has been already initiated by administrative activitites. It will be then rapidly implemented to project management, and progressively to all research activities in the unit. To support that important commitment, it is of premium importance that the permanent position for a quality research engineer (currently supported by CHRU), which was not granted this year by Inserm, is obtained next year.

Specific comments / Team 1

1. Recruitment of full time researcher.

Although an important part of our research is devoted to clinical studies, we fully agree that the lack of full time researcher has been and remains an important limitation for developing our translational projects. This point has been already addressed in part by the arrival of Team 2, as well through intense collaborations with the other UMRs of EGID. However, the recruitment of full time researchers will surely remain our priority during the next five years.

In 2015, Caroline Bonner, who joined our team 18 months ago after a PhD in Dublin and a year in Cochin (Catherine Postic team), will apply as Inserm CR. In close connection with team 2, she will further develop human islet cell biology in the research unit and more specifically will develop the sorting and biological assessment of human non beta islet cells (alpha / delta).

In parallel, we will continue to trace promising PhD students and deploy efforts to attract talentuous French and international post docs for preparing the recruitment of at least another full time researcher in the following years.

2. Minipig translational model

For the limited time available, we did not sufficiently emphasize our current efforts to develop translational science in the minipig model, particularly in the context of metabolic surgery.

During the past period, these efforts coordinated by Thomas Hubert (Veterinarian and MCU) in the context of islet cell therapy, have allowed us to master unique know-hows for the study of glucose metabolism in the adult minipig. The relevance of this chronic preclinical model has been already documented by several successful clinical translation of our findings. Intramuscular islet transplantation which was developed this way, is currently further optimized in the minipig, by co-transplantation of precursor endothelial cells, in collaboration with Georges Uzan (Villejuiff).

More recently, significant progress have been made by Robert Caiazzo (MCU) to develop a relevant preclinical model for the study of metabolic surgery (Verhaeghe et al. Eur Surg Res 2014). In parallel to the testing of new devices to replace surgery (Industrial partnership with Cousin Biotech), this unique model will be used to explore the mechanisms of the modulation of glucose absorption identified in our clinical

studies after GBP. Furthermore, an obese and hyperglycemic minipig is under development using high fat diet in conjunction with partial pancreatectomy.

Finally, to further extend these efforts and as suggested by the committee, we recruited in February a new post doc, Mehdi Daoudi PhD (formerly in Bart Staels' lab), to explore in this model and in close connection with our ongoing clinical studies, the cellular and molecular biology aspects associated with metabolic surgery.

Overall we envision that, at the opening of EGID building and its new extended minipig facility (2016), these comprehensive efforts will place our team in a unique and highly competitive position for the study of new interventional diabetes therapies in this relevant preclinical model.

3. Involvement of technical staff in basic translational projects

As noted by the committee, the production of human islets for clinical islet transplantation is a massive activity, which requires an abundant and highly experienced technical staff. On the other hand, human organ being by nature irregularly available, our production team is also available and largely implicated in translational research activities.

In that regard, our team regularly developed highly competitive models which included in the recent years, the efficient transfection of intact human islets, the purification of human alpha cell, or *in vivo* longitudinal study of normal islets in the context of insulin resistance (high fat diet or S961). Three important studies were recently based on these models and the work of the team technical staff: one in collaboration with Kathrin Maedler (Bremen) will appear soon in Nature Med, and two others are currently reviewed by major journals, one from Caroline Bonner from our team, another in collaboration with Markus Stoffel from IPFL.

In connection with team 2, these efforts will be amplified in the coming years. In 2014, we will initiate a close collaboration with Jean-Claude Henquin (Visiting Professor) to develop the dynamic functional assessment of human islets by perifusion. As suggested by the committee we will more clearly organize and allocate the activities of the technical staff between production and research activities.

Specific comments / Team 2

1. Stability of the group in the medium/long term

We carefully consider this crucial point which has been already prioritized by the UMR and EGID, as well as by Lille 2 University.

In addition to the two permanent positions of research engineers already allocated to Team 2, EGID recently confirmed a 300 KE specific fund to cover salaries and running costs of the team during the next two years, after the Chaire d'excellence ANR. In 2014, the UMR will prioritize the recruitment by Lille 2 University of one

assistant engineer in team 2, as well as a two year post doc position obtained from Lille Métropole.

In parallel, a pro active strategy has been initiated to secure external funding in the coming years. A first grant was recently confirmed by SFD for the study of the JNK3 signaling as a novel route whereby the GLP-1 mimetics exert their antidiabetic effects on beta cells. Two other grant applications are currently pending (ANR, ANSES) and these efforts will be intensified in the coming years. Negotiations have been also initiated under the umbrella of the SATT-Nord, to develop a collaborative industrial partnership on the development of therapeutic peptides and novel tools and reagents helping our projects.

Stabilization of the team will be actively pursued during the following years, aiming at the recruitment of one more assistant engineer, and to support the application of Hélène Ezanno, currently post doc in our team, as Inserm CR in 2016.

2. Risky project, alternative program

Our research program aims to design innovative strategies to combat beta cell death in the context of clinical islet transplantation and ultimately diabetes. To achieve this end, the team leader mainly dedicates its times to research activities whereas the teaching tasks have been discharged by 2/3 by the University. Our leading project allowed us to identify DLK/IB1/JNK3 as important targets to maintain beta cell function and survival. Relevant genetic mouse models, knocked out for DLK and JNK3, have been obtained in collaboration with S. Ohno, (Yokohama, Japan) and C. Bonny, (Lausanne), respectively. The results recently obtained confirm the importance of the two proteins in beta cells and glucose homeostasis. For this reason, we are now developing derivative peptides aiming at restoring the level of the signaling in beta cells, under diabetic condition. Importantly, the clinical relevance of strategies based on derivative peptides has been already documented in clinical trials for treating acoustic trauma and deafness.

Nonetheless, and as emphasized by the committee, these strategies remain risky. Therefore, we are also exploring alternative approaches. First, we are investigating the role of histones deacetylases and their respective inhibitors (many of them are currently used in clinical trials for cancer therapy) for beta cell survival. Furthermore, we are also investigating other available drugs, in original ways and other targets important for cell survival and function, which interplay or not with the JNK signalling. The funding recently obtained from SFD will foster our project on PKA and AKT signalling, elicited by the GLP-1 mimetics are major targets.

3. Interaction with team 1

The ultimate goal of our research project is the translation of innovative strategies to protect beta cell mass and function in the context of diabetes therapy. Importantly, beta cell protection is also of pristine importance in beta cell therapy both *in vitro*, prior to transplantation, and i*n vivo* in the recipient. In close connection with team 2, the most promising strategies identified in experimental models by our team will be progressively translated in the context of islet transplantation. For that purpose, we

will test these strategies in the different incremental models available : functional studies in porcine and human islets, both in vitro and in vivo following transplantation in immuno deficient mice, then in islet autotransplantation in the minipig. If expected results are confirmed, the most relevant strategies could be rapidly implemented in the clinic, at least during the preparation and culture of islets prior to transplantation and significantly improve recipient outcome. In return, the rapid roadmap from bench to bedside offered by islet transplantation will represent a unique plateforme for promoting our best strategies in the general context of diabetes therapy.

The expertise and experimental tools of team 2 will also significantly contribute to the translational projects of team 1. In the past months, our interactions and parallel experiments performed in ob-ob mouse and human models in the context of insulin resistance have recently boosted the study of SGLT2 function in alpha cells and led to a co-authored manuscript, now under review in a major journal.

Francois Pattou
Directeur
U-859 – Biothérapies du diabète.

Le Président de l'Université
Pr Xavier VANDENDRIESSCHE

Université Lille 2
Droit et Santé