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

Department for the evaluation of research units

AERES report on unit:

Integrated genomics and modelization of metabolic diseases

Under the supervision of the following institutions and research bodies:

Université Lille 2 – Droit et Santé

Centre National de la Recherche Scientifique

Institut Pasteur

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. Florent SOUBRIER, 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:	Integrated genomics and modelization of metabolic diseases
Unit acronym:	
Label requested:	UMR, UMR_S
Present no.:	UMR_S 8199
Name of Director (2013-2014):	Mr Philippe FROGUEL
Name of Project Leader (2015-2019):	Mr Philippe FROGUEL

Expert committee members

Chair:

Mr Florent SOUBRIER, Université Pierre et Marie Curie, Paris

Experts:

Ms Catherine ANDRE, Université de Rennes 1 (representative of CoNRS)

Ms Miriam CNOP, Université Libre de Bruxelles, Belgique

Mr Etienne LARGER, Université René Descartes (representative of the CNU)

Ms Maria MARTINEZ, Université Paul Sabatier, Toulouse

Mr Vincent MOOSER, Université de Lausanne, Suisse

Mr Jean-Francois TANTI, Université de Nice-Sophia Antipolois (representative of INSERM)

Scientific delegate representing the AERES:

Mr Jean ROSENBAUM

Representatives of the unit's supervising institutions and bodies:

Mr Regis BORDET, Université de Lille 2 - Droit et Santé

Mr Thierry GRANGE, Centre National de la Recherche Scientifique

Ms Brigitte JUDE (representative of Doctoral School n°446)

Ms Anne ROCHAT, Institut National de la Santé Et de la Recherche Médicale

1 • Introduction

History and geographical location of the unit

The unit is located at the institut Lille Pasteur. The group was created in Lille in 1995, as an emerging CNRS team, by the transfer of the team from the "Centre du Polymorphisme Humain" in Paris to the institut Pasteur de Lille. Subsequently, the CNRS unit became affiliated to Université Lille 2 as a University/CNRS Joint Research Unit (UMRS 8199). In 2010, the unit contributed strongly to the LABEX project "European Genomic Institute for diabetes" and to the EQUIPEX project "Lille Integrated Genomic Advanced Network-personalized medicine" (LIGAN-PM), that were both financed through the program "Innovation for the future".

A new team joined the unit in autumn 2013, directed by Mr Jean-Sebastien ANNICOTTE (PhD), DR INSERM.

The unit is now requesting a double affiliation to both CNRS and INSERM.

Management team

The lab is directed by Mr Philippe FROGUEL, assisted by a lab manager and three adminstrative managers, 2 from CNRS and one from the institut Lille Pasteur.

AERES nomenclature

SVE1_LS1

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	2	4
N2: Permanent researchers from Institutions and similar positions	7	6
N3: Other permanent staff (without research duties)	20	20
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	1
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	5	4
N6: Other contractual staff (without research duties)	16	12
TOTAL N1 to N6	**51**	**47**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	5	
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	8	7

2 • Assessment of the unit

Strengths and opportunities related to the context

The main strength of the unit relies on the expertise, the achievements, and the overall research activity of its director relying on efficient collaborators for realizing a pioneer activity in high throughput genetic analyses. Indeed, Mr Philippe FROGUEL has implemented a research project on genetics of diabetes and obesity which has generated all possible expected benefits in terms of scientific results and international recognition. The project of the unit is based on the collection of large cohorts of patients and controls for different types of diabetes and obesity (either familial forms or sporadic forms) that could be exploited for identifying susceptibility genes. Mr Philippe FROGUEL was the first to publish a Genome Wide Association Study (GWAS) on type 2 diabetes (T2D), introducing this approach specifically to metabolic diseases. Owing to a real sense of organization, the unit has been organized to allow the generation of a large series of genetic results and for their analysis by numerous, efficient and competent bioinformaticians and biostatisticians.

The unit benefits from a large network on the different diseases, and of a strong local environment for the collection of cases and families and has set up several cohorts.

The unit is strongly supported by local institutions (University, hospital, Institut Pasteur).

As a director of two research units, one in Lille, and one in London (Imperial College), the director has been able to use the complementarity of the two teams to generate more results and to organize a reciprocal support on some projects.

Weaknesses and threats related to the context

The posible weaknesses paradoxically comes from the organization of the unit. This very effective organization is based mainly on the direction and the initiatives of the single director, which does not facilitate the emergence of scientific projects led by established scientists of the unit. This has been justified by the monothematic (a single project for the unit) character of the unit. This organization can be conserved because it has been successful in achieving this major scientific contribution on genetics of diabetes and obesity, but it might be difficult for young and talented scientists to obtain the possibility of developing their own projects. This might also be a weakness because in the case of departure or unavailability of the director, the unit might have difficulties to survive since all projects are highly dependent on the director.

The usual democratic functionning of the unit has been weak until few months ago, when a unit seminar was organized. Efforts have been made in general to improve this aspect of the functioning of the unit.

The weakness might also come from the fact that the type of projects that has been performed during the last years (GWAS) is less in vogue, although several major results have been obtained using this approach. For this reason, the director has shifted his activities towards other types of investigations (rare variants with stronger phenotype effects, familial forms, functional studies).

Recommendations

The global assessment of the unit is extremely positive. This judgment is based on standard criteria that the unit fulfills. The two main changes planned: switch from a monothematic lab to a 2 team lab and switch from a “pure” genetic and statistic lab to more mechanistic and functional activities is a challenge. Strong interactions between the two teams and development of team 2 are highly encouraged. The rationale for the installation of Mr Jean-Sebastien ANNICOTTE is obvious and the committee is confident in the development of fruitful relationhips and efficient interactions.

3 • Detailed assessments

Assessment of scientific quality and outputs

The unit was represented in the previous period by the single team of Mr Philippe FROGUEL, and has produced major achievements in the field of genetics of diabetes and obesity. More than 200 publications have been published in leading journals (among them: Nature, Nature Genetics, Science). The unit has mainly contributed to the realization of GWAS on diabetes and obesity, and was indeed the first to publish one in 2007. In several publications, the input of the unit was however limited to providing cohorts for large international consortia. The Web of Science H-index of its director is 91.

One strength of the scientific project of the unit has been the ability to use different approaches of the genetics of type 2 diabetes and obesity, and not to be confined to a single approach. Indeed, beyond GWAS and using results issued from GWAS, the unit has explored the effects of rare variants (MTNR1B in T2D, GPR120 in obesity) and identified functional Copy Number Variants (CNVs) in obesity.

Therefore the unit has greatly contributed to defining the genetic architecture of T2 diabetes and obesity, using cutting-edge technologies. It is likely that some of the results obtained and published on GWAS should be reanalyzed in depth, in order to define their actual impact on the risk of the disease.

Assessment of the unit's academic reputation and appeal

The unit has received major awards and has been successful in several competitive call for proposals. For example, the director of the unit obtained an ERC, and the unit belongs to the LABEX EGID that was created under the initiative of unit director, to an EQUIPEX, and a post-doc obtained a “rising-star” award from the European Association for the Study of Diabetes. PhD students and post-docs are of good to excellent levels.

The unit has organized several international meetings in the field of metabolic diseases and the director of the unit is associate editor of the “Journal of Diabetes Investigation” and editorial advisor for “BMC Genomics”.

The unit has attracted new talents: a Lille University professor, an INSERM scientist coming with a small team for the next contract, and a biostatistician (assistant professor at Université de Lille).

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

The unit, as represented by its director, has many interactions with the socio-economic environment.

The unit is one of the 3 elements composing the European Genomic institute for Diabetes (E.G.I.D) which is supported by the investissements d’avenir, LABEX and has tight links with the EQUIPEX LIGAN-PM (sequencing and genotyping plarform). "The unit director is an opinion leader in the field of genetics of diabetes and obesity. He is requested as an expert by several national and international committees, has contracts with big pharmas, and numerous national and international fundings. He is also the director of a research unit at the Imperial College in London and is appointed as a scientific advisor in a foreign country willing to establish research on diabetes and obesity."

Assessment of the unit's organisation and life

The unit, constituted by so called “support teams” and “scientific teams”, as depicted in the organization chart provided is converging towards the director. In each scientific team, a senior scientist is present. Engineers and technicians can belong to both scientific and support teams.

The overall general climate in the unit seems good. Some points can be improved, such as setting up a laboratory council, and lab meetings should be scheduled more often. The organization of the unit does not favour the emergence of individual scientific projects by established scientists, who are asked to participate in the main project of the unit, led by its director. That has been clearly reaffirmed by the director, explaining that the unit is monothematic. This organization has been successful in terms of scientific output. Scientists willing to join the unit need to be aware of this organization.

Assessment of the unit's involvement in training through research

Five PhD theses have been achieved since 2009. Scientists of the unit participate in the teaching of the core curriculum of the doctoral cursus.

PhD students declare to be satisfied by their scientific education in the unit. They are invited to participate in French or European meetings. They have the opportunity to present their work, but not frequently. Some groups of the unit do not have regular lab meetings, however. They publish their work in good journals in general. At least one publication as a first author is required to defend a Ph.D. thesis.

Assessment of the strategy and the five-year plan

Two teams are planned to constitute the unit.

One of the research projects of team 1 (led by Mr Philippe FROGUEL) consists in searching for variants with major effects (mutations) in familial forms of diabetes and obesity by exome sequencing, and on the resequencing of drug target genes (500 genes in 5000 subjects) in order to find variants with significant effects on the phenotype, and that could be used for personalizing the treatment. Another project is dedicated to molecular analyses (transcriptomics and epigenomics) in tissues from patients undergoing obesity surgery and from patients with gestational diabetes. Finally, systems biology will be explored in the context of gene dosage in diabetes and obesity. One major project of the unit aims at building an induced pluripotent stem cells (iPs) model for functional B-cells defects in patients with monogenic forms of diabetes, in collaboration with another French group and the Harvard stem-cell Lab. There are no more GWAS projects envisioned for the future plan. It is surprising that no effort is invested by the team on the loci already identified in order to document the genetic and physiological mechanisms involved.

Team 2 (led by Mr Jean-Sébastien ANNICOTTE) will study the pathophysiological link between cell cycle genes and diabetes and obesity. This project will be addressed through the use of recombinant mice carrying mutated forms of transcription factors. Animals will be studied on several phenotypical aspects. Another program is focused on epigenetics of diabetes, in particular on the role of lysin acetyltransferase 2B (KAT2B) in diabetes. The KO mice for the orthologous gene (Pcaf-/-) show defective insulin secretion, and will be studied in detail. Other animal models will be used for functional studies, such as zebrafish and nematodes. Animal models will also be selected on the basis of results obtained by team 1.

According to the best scenario, strong interactions will occur between the two teams during the next five years, one team identifying important genes by exome sequencing or large scale gene resequencing, and the other one testing the gene functions in animal models. This scenario can be hampered by the fact that it may be tempting for the genetic team to collaborate with the group that has the best experience in the world on the gene. Furthermore, the team of physiologists can be engaged in other running projects and may not find resources for a collaboration that is usually urgent. Therefore, it is difficult to anticipate which interactions will indeed be developed between these two teams. However, the logic of this installation is obvious and the committee can be confident in the development of fruitful relationhips.

4 • Team-by-team analysis

Team 1 : Génomique et épigénomique des maladies métaboliques

Name of team leader: Mr Philippe FROGUEL

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	2	4
N2: Permanent EPST or EPIC researchers and similar positions	6	5
N3: Other permanent staff (without research duties)	20	20
N4: Other professors (PREM, ECC, etc.)	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	3
N6: Other contractual staff (without research duties)	15	11
TOTAL N1 to N6	**48**	**44**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	5	
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	7	6

• Detailed assessments

Assessment of scientific quality and outputs

Undoubtedly, the international field of T2D has gained significant benefits from the scientific production of the group leader. The first paper with the use of GWAS in these complex diseases was published in 2007 and it has really initiated the use of large cohorts and SNP genotyping methods for GWAS for diabetes and obesity.

The document states that UMR8199 has published 280 papers since 2008 on diabetes and obesity. The scientific production is outstanding. For example, since 2008, the group leader has coauthored 6 papers in Nature (1 as senior author), 35 in Nature Genetics (5 as senior author) and 1 in Science (senior author), etc.

Main achievements include:

GWAS analysis of quantitative trait, namely fasting blood glucose (Science 2008): this study of 330,000 SNPs in 654 normoglycemic individuals uncovered a SNP associated with fasting plasma glucose, but, curiously, not with diabetes risk. This SNP is close to MNTR1B, and a meta-analysis observed that the same SNP was associated with fasting plasma glucose, and diabetes risk (meta-analysis using data from 4 different populations). The product of MNTR1B, the melatonin receptor 2, is expressed in ¤ cells, but there was no direct proof of the involvement of this pathway (Nature Genetics 2009). Rare (allele frequency <0.1%) variants of the MTNR1B genes were associated with T2D, including half of them coding for non-functional isoforms of the receptor (Nature Genetics 2012). A link between diabetes and circadian rhythm was proposed. The paradigm is thus that rare pathogenic variants can contribute to the pathogenesis of common forms of diseases. The frequency of variants with abrogated melatonin binding was however 0.22% in patients with diabetes and 0.13% in control subjects.

Demonstration of a gene dosage effect of a region of chromosome 16 (through CNV), such that deletion of the region on one allele was associated with severe obesity and duplication of the same region was associated with extreme leanness in a complex syndrome, in which developmental or intellectual disabilities and psychiatric disorders were the predominant symptoms at presentation (Nature 2010, Nature 2011).

Other main achievements include participation to wide international consortia of GWAS of obesity and type 2 diabetes (30 papers, including 23 in Nature Genetics).

Assessment of the unit's academic reputation and appeal

The unit belongs to large international collaboration networks. Scientific involvement of the team in international projects is excellent, with coordination and leading evidence in most projects.

Grants are described in annex 37 : 18 Research “grants” for team 1 of which 12 are led by the group leader : 1 Equipex, 1 Labex, 1 ERC 1 IT Diab (from OSEO), 2 ANR. The budget of these grants range from 75 K€ to 8000 K€ ! (between 2009 -2019).

The UMR 8199 has multiple collaborations in European programs (3 projects: IMI, IMIDAI and Direct) and has participated in this context to meta-analyses that have been published in high-impact journals.

The group leader and another scientist have received prestigious European awards. The lab is a founding member of the EGID federation, which was qualified as a LABEX (“Laboratoire d’Excellence”) and is tightly linked to an Equipex (“Equipement d’excellence”) from the “Investissements d’Avenir” funding program.

Eight researchers with tenure positions have joined the lab and 6 have left it.

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

The EQUIPEX “LIGAN médecine personnalisée” is used for both academic and for-profit institutions. The document states that it is used for 1/3 time for service provision out of the EGID federation. The biotech GENOSCREEN company, founded by people originating from the UMR, seems to be the main “private” user.

Assessment of the unit's organisation and life

An annual Seminar was organized in 2013, during which there was a discussion about the increase in CDD (temporary positions), the increase in the work burden, and the cohesion of people in the unit, faced with an increased work load. The report of the external consultant indicated that people agreed on the fact that the lab benefits from its leader's creative efforts and remains dependent on these efforts. The consultant has not identified any dramatic concerns from the people to change the present organization, except the demand to establish regular laboratory council meetings.

In order to improve the applications for permanent positions at INSERM or CNRS from young scientists of the unit, it is important that candidates can present clearly their own contributions in large collaborative studies, and can propose a scientific project in which they will be able to put a significant impact.

Assessment of the unit's involvement in training through research

The unit is part of the École Doctorale Biologie-Santé # 446 (Université de Lille), and participates in the research master by animating 9 days teaching on diabetes, obesity and "cardiometabolic diseases". As part of the EGID federation the unit has created the annual EGID seminar, with a wide national audience.

Five students have defended their PhD thesis in the 2009-2013 period. Five students are in the second to third years of their thesis project. Four post-doc researchers are currently in the lab. Five have left the unit between 2011 and 2013.

Assessment of the strategy and the five-year plan

Main objectives of the team:

1/ Rare monogenic forms of diabetes:

The first task is to describe new genes associated with monogenic forms of diabetes: MODY (T2D with a dominant mode of inheritance), and NDM (Neonatal diabetes) through exome sequencing of quartet (for MODY) and trios (for NDM). The group leader and his team have realized that the GWAS strategy has been intensively exploited and have decided to mainly shift back to monogenic forms of diabetes and obesity, in which mutations have a stronger effect that is easier to identify and characterize. They also intend to determine the sequence of hundreds of genes in a large cohort of patients in order to find variants with an intermediate impact on the phenotype, enabling secondary association studies based on these variants. They will also use the same approaches for severe monogenic obesity.

Models of induced pluripotent stem cell (iPSC) from different types of monogenic diabetes, including MODY-X (patients with a MODY phenotype but no known mutation), to investigate how such cells can be differentiated to insulin-secreting B-cells to study molecular defects, reasoning that all known MODY-mutations affect insulin secretion. The technique is however not available in the lab and the project consists in setting up the technique in collaboration with expert labs.

A similar project will be developed for rare monogenic forms of obesity.

2/ Large scale targeted resequencing of T2D drug targets. This project has the originality to use a highly sensitive method to detect variants (Raindance technology in nano lipidic droplets and NGS) on 500 genes in 5000 patients. The strategy consists in searching for rare genetic variants with strong biologic effects, followed by functional analysis of these variants. GPCR and genes involved in the melatonin and clock genes will be specifically targeted.

3/ Genetic and epignetic approaches will be developed on patients undergoing obesity surgery and in patients with gestational diabetes. In both cases, tissues are available (taken at surgery in the first case, and placenta in the second case) and transcriptomics and epigenetics studies can be performed on these samples.

4/ A system biology approach will be developed specifically on gene dosage effects in obesity. This relationship will be used as a paradigm for the further development of system biology. The CNV of the amylase gene will be studied for its relationships with obesity and with the gut microbiota.

The conceptual basis of these projects is sound and represents an interesting development of the previous projects.

These different projects are highly interconnected and will be done in close collaboration with team 2 and will use methods that are already implemented, except for iPS and aspects of system biology. There is no doubt that the group leader will use skills present in his two labs to enable these projects to succeed.

Conclusion

- **Strengths and opportunities:**

The group leader has shown in the last 20 years his ability for achieving ambitious projects, raising funds, building efficient labs and has an outstanding list of realizations in the field of genetics of diabetes and obesity; one can thus be extremely confident that he can reach the next scientific targets.

The previous project was diversified within the field genetics of diabetes and obesity. The GWAS strategy and the cohorts were well exploited, allowing rare variants with significant effects to be identified.

The previous project was the source of a rich scientific production and the new project is well articulated with the skills of the unit.

- **Weaknesses and threats:**

There are some basic questions which need to be addressed when dealing with genetics of diabetes:

-The main determinant is age, and the peak of incidence is between 50 and 70 years. Thus the age at which control subjects and non-affected relatives are studied is critical.

-While part of the project is based on epigenetic studies, it is not really clear how the team will deal with the identification of the respective part of genetically- and culturally - inherited risks, since recent analyses indicate that the main determinant of type 2 diabetes is not genetic.

-These important points should be taken into account for interpreting data.

-The GWAS strategy seems to be withdrawn, but results already obtained with the GWAS are not discussed in depth. Shifting to NGS is the most appealing option, although the conceptual basis is just described as a search for rare variants, based on their experience with the melatonin receptor 2. The strength of the lab has been its capacity in progressing with the techniques of DNA sequencing and bioinformatics and statistics. However deriving iPSC from PBMC is completely beyond the skill of the lab, making the lab dependent on other labs until the technique is implemented in the lab.

- **Recommendations:**

In conclusion, the project is convincing, and the group leader has shown that he was able to lead and achieve ambitious projects.

The recommendations are to pursue innovative projects using a variety of approaches, as done before, to tight the link with the new team, and to facilitate the emergence of projects led by scientists of the unit.

Team 2: Bases Moléculaires et Modélisation du Diabète et de l'Obésité

Name of team leader: Mr Jean-Sébastien ANNICOTTE

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

This new team was created in 2012 with the arrival of the team leader Mr Jean-Sébastien ANNICOTTE from Montpellier. Hence, there are no previous results from this team as such, even if some initial results obtained in Lille are very encouraging and support the feasibility of the project. The team has a good track record of publications (16 for the 2009-2013 period for a total of 37 publications since 2001). Some of them were published in outstanding journals (Nature Cell Biology, JCI). The main achievement of the research of the project leader was the demonstration that transcription factors regulating the cell cycle are also key to the adapted metabolic response of beta cells and muscle. These original data have unveiled a strong interconnection between cell cycle and the control of metabolism and suggest that dysfunction in such regulation may participate in the development of the metabolic complications of obesity. This hypothesis will be tested in the project by using KO mice for E2F1. Thus, the background and expertise of the project leader fit perfectly with the context of the proposed project. He is well-trained and has now to prove his capacity to establish himself as an independent researcher and to lead a team.

Assessment of the unit's academic reputation and appeal

This young team has already attracted one postdoc and one Ph.D student demonstrating a good visibility of the team. In the past the team leader has obtained charity grants (SFD, ARD) and local grants (Programme chercheur d'Avenir Langudedoc Roussillon). The team has obtained a charity grant (SFD) and funding from the EGID LABEX to start the development of the project. Collaborations with other academic teams have been developped. The team will benefit from the integration in the EGID LABEX and this opportunity should be exploited to increase its visibility.

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

Not applicable for this emerging team.

Assessment of the unit's organisation and life

This new team is relatively small with five persons (the team leader, a postdoc, a Ph.D student and two engineers/technicians) involved in the project.

Assessment of the unit's involvement in training through research

Since it is a new team, the training activity is limited in Lille, but a Ph.D student and a Master student were already recruited.

Assessment of the strategy and the five-year plan

The research program is the continuation of the project that the team leader has developed in his former laboratory concerning the involvement of the regulators of the cell cycle in the control of metabolism. The project will be developed along three major axes:

. Role of three cell cycle regulators E2F1, CDK4 and CDKN2A in the adapted metabolic response and development of beta cells and their implication in the development of diabetes. The role of these proteins in other tissues controlling the metabolic homeostasis (muscle, liver, adipose tissue, hyptohalamus) will be also investigated.

. Role of epigenetic modifications in the control of glucose homeostasis and the development of type 2 diabetes. In this context, the team will focus on an interesting target, Pcaf, a lysine acetyl transferase in the function and development of beta cells as well as in the function of insulin sensitive tissues. Sound preliminary data about a role of this enzyme have been already obtained.

. Relationship between the regulation of cell cycle diabetes and cancer. In this context, the role of E2F1 in the endocrine cells for the development of pancreatic adenocarcinoma will be studied. This part of the project is out of the scope of the research unit.

The questions that are addressed are relevant. The relationship between cell cycle, epigenetic modifications and regulation of metabolic homeostasis is an emerging theme that is certainly going to provide novel insights on the development of the metabolic complications of obesity and diabetes and on the relations between environment and gene expression in this context. The experimental design is carefully thought. The different approaches combining cell and animal models as well as human genetics in collaboration with team 1 should deliver very relevant data. The problem that can be raised is the relevance of the mouse model of beta-cell regeneration to human diabetes.

Care should be taken to avoid dispersion in order to remain competitive in the field. Indeed, it is proposed to generate and to study different original models of mice with tissue-specific invalidation of the different proteins (E2F1, CDK4, CDKN2A, PCAF) in beta cells, liver, muscle, fat and hypothalamus. This proposal seems overambitious for the current team size of 5 people. A focus on beta cells only seems more adapted to the size of the team and even in this conditions, it seems unrealistic to manage in parallel the study of five different mouse strains. Thus, the team leader should clearly make a priority in the different items of the project.

Conclusion

- **Strengths and opportunities:**

A promising group leader with a strong expertise in the metabolic field which is complementary to the expertise of team 1 in the genetic field. The research project is timely and addresses an important question. The expertise to develop it is available, being either part of the past experience of the team leader or the subject of collaborative projects with expert groups. The good complementarity between the two teams is obviously an asset for developing functional genomic approaches in the unit, a major objective for the next years. Because the project is very ambitious, the enrolment of new collaborators and the stabilization of the technical staff are an absolute priority.

- **Weaknesses and threats:**

Like each team leader in the position of setting up his own group, the team leader will have to face a delicate transition period during which he will have to hire competent collaborators and develop his research project in a competitive field. However, this is not a weakness but rather the challenging situation that every new team leader has to cope with. However care should be taken to avoid dispersion in the project because as presented the project seems overambitious for the current size of the team.

- **Recommendations:**

It is important that this group prioritizes its projects, in order to be competitive. Indeed, the team is small and the number of projects too large, and the strength and ardour of the team leader may not be sufficient to achieve the projects.

Because the project is very ambitious, the enrolment of new collaborators and the stabilization of the technical staff are an absolute priority.

It is of key importance for this team to obtain national or European grants in order for the development of the project, although local support can be also envisioned.

5 • Conduct of the visit

Visit date:

Start: Tuesday 17th, December, 2013, at 9.00 a.m.

End: Tuesday 17th, December, 2013, at 4.45 p.m.

Visit site: Institut Lille Pasteur

Institution: Institut Lille Pasteur

Address: 1 rue du Pr Calmette, 59019 Lille.

Conduct or programme of visit:

09h30	Accueil du comité d'experts
10h00	Huis clos - Présentation de l'AERES au comité d'experts par le Délégué Scientifique (DS) *Auditoire : membres du comité d'experts, DS*
10h30	Devant l'unité, présentation du comité d'experts et présentation de l'AERES par le DS
10h40	Présentation globale de l'unité par son directeur, bilan et projet (discussion incluse)
11h15	Pause café
11h15	Présentation de l'équipe 1 (discussion incluse)
11h55	Présentation de l'équipe 2 (discussion incluse)
12h35-14h00	Déjeuner
14h00	Session de rencontre avec le personnel permanent et non permanent Le comité se répartit en trois sous-groupes qui travaillent en parallèle **- Rencontre avec les ITA titulaires et CDD** *Auditoire : membres du comité d'experts, DS* **- Rencontre avec les doctorants et post-doctorants et/ou CDD « chercheurs »** *Auditoire : membres du comité d'experts, DS* **- Rencontre avec les chercheurs et enseignants chercheurs titulaires** *Auditoire : membres du comité d'experts et DS, sans la Direction, ni les responsables d'Equipes*
14h30	Rencontre avec les représentants des Tutelles (Lille 2, CNRS, Pasteur Lille, Inserm) *Auditoire : membres du comité d'experts, DS*
15h00	Rencontre avec le directeur de l'unité (et chef de l'équipe 1) et le chef de l'équipe 2 *Auditoire : membres du comité d'experts et DS*
15h15	Rencontre avec le représentant de l'École Doctorale M. Bernard SABLONNIERES *Auditoire : membres du comité d'experts et DS*
15h30	Réunion du comité à huis clos *Présence : membres du comité d'experts et DS*
17h30	Fin de la réunion

Specific points to be mentioned:

Besides those already mentioned, several people participated to the meeting with governing bodies representatives:

Mr Patrick VERMERSCH vice-dean for research at the faculty of medicine

Mr Samir OULD ALI, Local representative for Inserm

Ms Françoise PAILLOUS, Local representative for CNRS

Mr Régis FIEVE, Responsible for medical research at CHU de Lille

Ms Fabienne JEAN, manager for research at institut Lille Pasteur

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 4 mars 2014

V/Réf. : E2015-EV-0593560Z-S2PUR150007624-006352-RT

Objet : Observations de portée générale sur le rapport d'évaluation de l'unité *Integrated genomics and modelization of metabolic diseases.*

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 *Integrated genomics and modelization of metabolic diseases,* pour la qualité de l'évaluation effectuée le 17 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 *Integrated genomics and modelization of metabolic diseases.*

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

Pr. Xavier VANDENDRIESSCHE

CNRS UMR 8199
Génomique et Maladies Métaboliques
Directeur : Pr. Philippe FROGUEL
CNRS, Université Lille 2 et Institut de biologie et Institut Pasteur de Lille

Lille, le 3 Mars 2014,

Observations concernant le rapport d'évaluation de l'UMR8199 par l'AERES

Nous remercions le comité de l'AERES pour son travail en profondeur et pour la richesse de ses remarques. Nous avons été très sensibles à sa conclusion page 4 dernier paragraphe "l'évaluation globale de cette unité est extrêmement positive".

Nous sommes conscients de l'importance de faire émerger des jeunes chercheurs (page 4). Le passage à une UMR bi-équipe peut aider à diversifier nos talents. Concernant l'équipe de génétique de l'UMR8199, nous souffrons du mode de recrutement national par commissions disciplinaires rigides par les EPSTs et des orientations actuelles des commissions Inserm et sections CNRS de génétique, physio-pathologie (Inserm) génomique et physiologie (CNRS) qui rejettent largement nos candidats (sans même désormais leur laisser la possibilité d'être audités) pour des raisons qui n'ont aucun rapport avec la qualité de leur CV et l'excellence de leur projet (en général reconnus comme très bons par les rapporteurs des jurys des EPSTs mais dont la nature trans-disciplinaire à la fois fondamentale et translationnelle, génomique à visée physio-pathologique les fait classer "hors champ" par les différents jurys de recrutement qui se renvoient la balle).

L'apport de notre UMR aux efforts de consortia post GWAS n'est pas d'amener des cohortes mais de contribuer à l'analyse statistique des données génotypiques (par exemple imputation de données génétiques plus précises), contrairement à ce qui est écrit page 5 paragraphe 1. Par ailleurs, nous nous excusons de ne pas avoir été assez clair sur nos efforts concernant les loci "déjà identifiés par GWAS" par nous et d'autres (page 6 paragraphe 3): l'effort de reséquençage des gènes "candidats" que nous comptons engager porte aussi sur tous les gènes identifiés par GWAS comme nous l'avons déjà fait pour le récepteur de la mélatonine. Ainsi la remarque similaire p 10 avant dernier paragraphe n'est pas fondée, d'autant plus que nous collaborons étroitement avec le Dr Prokopenko, *senior lecturer* à Imperial College pour l'analyse des effets pleiotropiques de ces loci (et l'imputation de variants rares non codants de ces loci). Seul le manque de temps nous a conduit à ne pas présenter cet aspect de nos recherches génétiques post GWAS lors de la visite du jury d'AERES.

Il y a une erreur factuelle p 8 paragraphe 2 portant sur l'absence d'affiliation "UMR8199" de Philippe Froguel dans l'article dans Nature Jacquemont et al, 2011. Après vérification de la page 485 du volume 478 du journal Nature Philippe Froguel porte l'affiliation 109 qui correspond bien a l'UMR8199. Il y a donc bien eu, parmi les publications majeures de l'UMR8199, deux articles dans Nature avec Philippe Froguel représentant l'UM8199 en co auteur principal (senior).

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Concernant l'équipe 2, nous sommes conscients de l'aspect ambitieux des projets présentés. Cela nous semble être justifié par la durée du projet scientifique, qui, sur une durée de 6 ans, demande d'être compétitif, innovateur et donc ambitieux. Cependant, nous évitons de nous disperser. Comme suggéré par le comité, une réflexion concernant les projets à développer en priorité a déjà été établie. La connaissance de l'état d'avancement de nos travaux, associée au potentiel scientifique et technologique de notre UMR et de nos collaborateurs nous permet de développer les projets dans les meilleures conditions, ce qui nous permettra de les publier dans les meilleurs journaux. D'autre part, nous pensons que la diversification de nos projets en modélisation (Zebrafish par exemple) sera rendu possible grâce à l'apport d'EGID, et des possibilités d'attractivité de spécialistes dans ces domaines.

En lien avec ces remarques, nous sommes également conscients de l'absolue nécessité de recruter d'excellents collaborateurs pour développer ces projets, de les stabiliser ainsi que notre personnel technique. Bien que cela fasse partie des priorités de notre UMR, nous ne pouvons décider pour nos tutelles, et notre volonté ne résiste pas à une politique de faible recrutement sur postes permanents.

Enfin, en accord avec le comité AERES, nous répondons régulièrement à des appels d'offre de financements nationaux et européens, afin de développer les projets et de recruter des collaborateurs sur les projets développés.

Professeur Philippe Froguel

Le Président de l'Université

Xavier VANDENDRIESSCHE

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