Research evaluation

REPORT ON THE RESEARCH UNIT:
Metabolic functional (epi)genomics and molecular mechanisms involved in type 2 diabetes and related diseases

UNDER THE SUPERVISION OF THE FOLLOWING INSTITUTIONS AND RESEARCH BODIES:
Université de Lille
Centre hospitalier régional et universitaire de Lille - Chru Lille
Centre national de la recherche scientifique - CNRS
Institut national de la santé et de la recherche médicale – Inserm
Institut Pasteur Lille

EVALUATION CAMPAIGN 2018-2019
GROUP E

In the name of Hcéres[1]:	In the name of the experts committee[2]:
, President	, Chairman of the committee

Under the decree No.2014-1365 dated 14 November 2014,

[1] The president of Hcéres "countersigns the evaluation reports set up by the experts committees and signed by their chairman." (Article 8, paragraph 5);

[2] The evaluation reports "are signed by the chairman of the experts committee". (Article 11, paragraph 2).

This report is the sole result of the unit's evaluation by the expert committee, the composition of which is specified below. The assessments contained herein are the expression of an independent and collegial reviewing by the committee.
Tables in this report were filled with data provided by laboratories and supervising bodies in the unit's application and in the Excel files "Données du contrat en cours" and "Données du prochain contrat".

UNIT PRESENTATION

Unit name:	Metabolic functional (epi)genomics and molecular mechanisms involved in type 2 diabetes and related diseases
Unit acronym:	n/a
Requested label:	UMR
Application type:	Restructuration
Current number:	8199
Head of the unit (2018-2019):	Mr Philippe FROGUEL
Project leader (2020-2024):	Mr Philippe FROGUEL
Number of teams:	2

EXPERTS COMMITTEE MEMBERS

Chair: Mr Hans-Ulrich HARING, Medizinische Fakultät Tübingen, Germany

Experts:

Mr Marc AUBRY, Université de Rennes (supporting personnel)

Mr Etienne LARGER, Université Paris Descartes (representative of CNU)

Ms Susan OZANNE, University of Cambridge, United Kingdom

Mr Xavier PRIEUR, Inserm Nantes (representative of Inserm CSS)

Mr Hugues ROEST CROLLIUS, CNRS Paris (representative of CoNRS)

HCÉRES REPRESENTATIVE

Mr Jean-Paul LALLÈS

REPRESENTATIVES OF SUPERVISING INSTITUTIONS AND BODIES

Mr Raymond BAZIN, Inserm

Mr Frédéric GOTTRAND, Chru de Lille

Ms Fabienne JEAN, Institut Pasteur de Lille

Mr Domenico LIBRI, CNRS

Mr Lionel MONTAGNE, Université de Lille

INTRODUCTION

HISTORY AND GEOGRAPHICAL LOCATION OF THE UNIT

The unit is located at the Lille Pasteur institute. The unit 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 Lille Pasteur institute. Subsequently, the CNRS unit became affiliated to Université Lille 2 as a University/CNRS Joint Research Unit (UMR_S 8199). In 2010, the unit contributed strongly to the Labex project "European Genomic Institute for Diabetes" and the EquipEx genomic platform LIGAN-Personalised Medicine (LIGAN-PM) that were both financed through the program "Innovation for the future".

MANAGEMENT TEAM

Director of the unit: Philippe Froguel

HCÉRES NOMENCLATURE

SVE2_2; SVE5_1

SCIENTIFIC DOMAIN

The unit is dedicated to genetics and epigenetics of diabetes and obesity, functional genomics of diabetes and the molecular pathophysiology of diabetes by the generation and analysis of *in vivo* rodent models of metabolic diseases. The unit develops translational concepts to allow individualized therapies of obese and diabetic patients. The unit develops and manages the EquipEx LIGAN-PM genomic core lab.

UNIT WORKFORCE

	Unit workforce	
	Integrated Genomics and Metabolic Diseases Modeling	
Active staff	**Number 30/06/2018**	**Number 01/01/2020**
Full professors and similar positions	4	5
Assistant professors and similar positions	3	5
Full time research directors (Directeurs de recherche) and similar positions	1	1
Full time research associates (Chargés de recherche) and similar positions	2	5
Other scientists ("Conservateurs, cadres scientifiques des EPIC, fondations, industries, etc.")	2	2
High school teachers	0	0
Supporting personnel (ITAs, BIATSSs and others, notably of EPICs)	26	27
Permanent staff	**38**	**45**

Non-permanent professors and associate professors, including emeritus	0	
Non-permanent full time scientists, including emeritus, post-docs	6	
PhD Students	4	
Non-permanent supporting personnel	16	
Non-permanent staff	**22**	
Total	**60**	

GLOBAL ASSESSMENT OF THE UNIT

The unit is considered to be one of the world leading laboratories addressing the genetic architecture of obesity and type 2 diabetes. This statement was the key result of the preceding evaluation in 2013. However, the 2013 review identified a number of issues that were thought to further improve the excellent quality of the unit. In the meantime, the head of the unit has responded to these recommendations and has initiated a number of changes with respect to the institutional structure and the faculty which have clearly further strengthened the visibility and the standing of the unit in the scientific field.

Research of metabolic diseases has tremendously profited from the results of genome-wide association studies which provided hundreds of novel genes which might contribute to the pathogenesis of these diseases. The next, however more difficult task is now to understand the biology behind these genes. The measures initiated by the head of the unit will prepare it to face this challenge and to stay at the forefront in the field of metabolic diseases.

Among many other scientific achievements, the unit has essentially contributed to the understanding of the control of body weight regulation via the leptin receptor-MC4R axis. This has paved the way to a more personalized therapy of obese patients carrying a rare mutation in the MC4R. This is proof of principle that the unit follows a successful translational concept of research. A particular strength of the unit is the development of methods which allow the implementation of the concept in clinical practice.

Overall, the unit has an impressive scientific output and is world leading in genetics of metabolic diseases and their translation into prediction, prevention and therapy of diabetes and obesity. The unit is publicly visible and uses the popularity of its head for fundraising, thereby efficiently supporting translational concepts. The unit is attractive for international PhD students, visiting fellows and postdocs, for example with schemes in place to provide support for initial accommodation costs when moving to Lille. Young investigators have excellent opportunities to shape their own scientific carriers thanks to their excellent publications.

The unit provides excellent opportunities for researchers of all ages and genders. The unit´s life is well organized and allows vivid exchange of data and ideas.

The scientific strategy of the unit is excellent and will provide clinically relevant results for personalized therapy of metabolic diseases.

DETAILED ASSESSMENT OF THE UNIT

UNIT'S RESPONSE TO PREVIOUS RECOMMENDATIONS

The former evaluation has led to the conclusion that the unit is excellent and belongs to the world leaders in genetics of metabolic diseases. There were a number of recommendations how to further improve the standing of this excellent unit. Overall the unit has efficiently responded to these recommendations and has even further developed its scientific profile.

The most important steps were:

- Concentration of working groups in one building;
- Marked increase in the number of scientists in the institute;
- Recruitment of renowned experts both in genetics and in functional characterization of genes in animal models;
- The interaction of the two teams of the unit was further strengthened by mutual exchange of research data and concepts. This will allow in the future to develop truly complementary projects between teams. Hypotheses derived from the genetic results of team 1 can be used to develop mouse models in team 2 which elucidate the mechanisms behind gene variants;
- Updating of the genomics core;
- Establishment of a human iPSC platform to study the role of mutations in vitro made possible by strategic recruitment;
- Foundation of novel and synergistic regional (EGID) and transregional (DIAGENIL) research collaborations.

The review board identified a number of issues that were thought to further improve the excellent quality of the unit. The board has criticized the strict organization of the unit with a single director, the lack of networking within the unit and the strict monothematic focus of the unit. The unit has responded to these points. The unit recruited and is further recruiting a number (n=8) of new scientists thereby strengthening the expertise and broadening the governance of the unit and the project portfolio. In addition this facilitates the emergence of scientific projects both by established scientists and new investigators addressing another key recommendation made by the previous visiting group. A key recommendation of the previous review group was the move from the monothematic character of the unit to a two-team approach. This has been successfully developed with the two teams well established, one focused on genetics and epigenetics of diabetes and obesity and the second on the molecular basis and modeling of diabetes and obesity. Importantly they are now also both based in the same building Furthermore the unit established novel research networks (EGID and DIAGENIL). This will improve the visibility and the standing of the unit in the scientific field.

CRITERION 1: QUALITY OF SCIENTIFIC OUTPUTS AND ACTIVITIES

A – Scientific outputs and activities, academic collaborations, reputation and appeal

Scientific outputs and activities, academic collaborations, reputation and appeal From 01/01/2013 to 30/06/2018	Integrated Genomics and Metabolic Diseases Modeling
Articles	
Scientific articles	144
Scientific articles with last authorship *(Biology only)*	46
Review articles	14
Other articles (professional journals, etc.)	3
Clinical articles	2
Books	
Scientific book edition	0
Book chapters	3

Meetings	
Meeting abstracts	31
Meetings and congress organisation	11
Electronic tools and products	
Software	0
Databases	0
Tools for decision making	0
Cohorts *(Biology only)*	2
Instruments and methodology	
Prototypes	0
Platforms and observatories	0
Other products	
Artistic creations	1
Movie or theatre play creation	0
Movies	0
Editorial activities	
Participation to journal editorial boards (books, collections)	7
Peer reviewing activities	
Reviewing of journal articles	yes
Grant evaluation (public or charities)	yes
Participation to lab site visit committees (Hcéres, etc.)	yes
Participation to institutional committees and juries (CNRS, Inserm, etc.)	yes
Academic research grants	
European (ERC, H2020, etc.) and international (NSF, JSPS, NIH, World Bank, FAO, etc.) grants	8
National public grants (ANR, PHRC, FUI, INCA, etc.)	15
Local grants (collectivités territoriales)	0
PIA (Labex, Equipex, etc.) grants	2
Grants from foundations and charities (ARC, FMR, FRM, etc.)	18
Visiting senior scientists and post-docs	
Post-docs	10
Visiting senior scientists	1
Scientific recognition	
Prizes	2
Distinctions	0

IUF members	0
Chair of learned and scientific societies	yes
Invitations to meetings and symposia (out of France)	> 50
Members' long-term visits abroad	0

Strengths

A strength of the research of the unit is to address key questions by combining international cohorts with the high throughput genetics platform of the unit. The unit continues to publish clinically relevant data and concepts in high ranking journals (*Nat Med, Nat Genet, Nat Rev Endocrinol, Cell Metab*) as leading authors. The invitation of a number of members from team 1 to be chairs of sessions in the top international Diabetes meetings (ADA, EASD, IDF) and the Director to speak at these meetings reflects their high international standing. The Director is on the editorial board of top journals in the field (*Cell Metabolism* and *Molecular Metabolism*) reflecting his international standing. Impressive amounts of money have been raised by the unit over the evaluated period: ANR > 3 million € (3 grants as coordinator); PIA > 7.6 M€; ERC > 1.5 M€ (1 consolidated grant and 1 starting grant); EU projects > 0.9 M€; other public funding > 2.6 M€; industrial contracts > 1 M€, etc. Post-docs were essentially from abroad (U.K., Argentina, Mexico, Soudan).

Weaknesses

The publication record has quantitatively dropped during the evaluation period. This is probably explained by the transition of the genetic field from the GWAS to the post-GWAS era. The newly created team 2 has published 10 papers; the effort of production should be maintained and amplified.

The unit has no institutionalized interaction with clinical partners to establish phenotyped cohorts in Lille. The head of the unit is aware of this problem and develops currently an interdisciplinary platform.

Assessment of scientific outputs, reputation and appeal

The unit has an impressive and outstanding scientific output. The unit is world leading in genetics of metabolic diseases and their translation into prediction, prevention and therapy of diabetes and obesity.

B – Interactions with the non-academic world, impacts on economy, society, culture or health

Interactions with the non-academic world, impacts on economy, society, culture or health From 01/01/2013 to 30/06/2018	
Socio-economic interactions / Patents	
Invention disclosures	2
Filed patents	2
Accepted patents	1
Licenced patents	0
Socio-economic interactions	
Industrial and R&D contracts	6
Cifre fellowships	1
Creation of labs with private-public partnerships	0

Start-ups	0
Clinical trials	0
Expertise	
Consulting	0
Participation in expert committees (ANSES, etc.)	yes
Legal expertise	0
Expert and standardization reports	0
Public outreach	
Radio broadcasts, TV shows, magazines	9
Journal articles, interviews, book edition, videos, etc.	2
Other popularisation outputs	no
Debates on science and society	3

Strengths

The unit is very present in public media promoting disease awareness. The unit successfully developed very innovative methods and collaborations with private companies (e.g. Sanofi) and obtained a CIFRE. The unit has two on-going patents and one accepted, which is good for a unit of this size. The two invention disclosures are also impressive.

Weaknesses

The team leader has successfully addressed clinically relevant questions in the past by collaboration with existing cohorts of international collaborators. This however limits the questions which can be addressed in the future. To widen the spectrum of clinical investigations the establishment of clinical trials with deep phenotyping would be desirable.

Assessment of the interactions with the non-academic world

The unit is publicly visible and uses the popularity of its head for fundraising, thereby efficiently supporting translational concepts.

C – Involvement in training through research

Involvement in training through research From 01/01/2013 to 30/06/2018	
Educational outputs	
Books	0
E-learning, MOOCs, multimedia lessons, etc.	0
Mean number of publications per student *(Biology & Science and technology only)*	2
Training	
Habilitated (HDR) scientists	7
HDR obtained during the period	1

PhD students	12
Defended PhDs	8
Mean PhD duration	36 months
Internships (BTS, M1, M2)	101
Education	
Courses with international label (ERASMUS, etc.)	0

Strengths

Due to the international visibility of the head of the unit, it is very successful in recruiting promising PhD candidates, visiting fellows and postdocs from all over the world (e.g. U.K., Belgium, Malta, China). The mean during of a PhD of 36 months is very impressive and the fact that on average they publish two papers is a very admirable statistic and much higher that many students at other institutions (e.g. *Nat Genet, Cell Rep*). Most PhDs have got positions of post-docs (in France and the US) while one got a position of Assistant-Professor and another one a position of research engineer. Young investigators have excellent opportunities to develop their own scientific carrier, thanks to their excellent publications (e.g. *Nat. Genet*. 2018).

Weaknesses

None

Assessment of the involvement in training through research

The unit is attractive for international PhD students, visiting fellows and postdocs. The publication record shows that young investigators have excellent opportunities to develop their own scientific carrier.

CRITERION 2: UNIT ORGANISATION AND LIFE

Unit organisation and life From 01/01/2013 to 30/06/2018	
Women/men ratio in the unit	0.51
Women/men ratio among unit scientists	0.73
Women/men ratio among unit PhD students	0.33
Women/men ratio among team leaders, unit head and deputy heads	0.50

Strengths

The gender distribution is in the expected range. The unit´s governance is transparent and includes a lab council and a steering committee. Furthermore internal seminars dedicated to project progress reports involving both teams are monthly organized and stimulate the scientific life of the unit.

Weaknesses

The ISO 15189 international standard that specifies the quality management system requirements particular to medical laboratories is costly to set up and maintain. As this standard is relative to medical laboratories and not academic research units, its implementation in UMR 9199 will need the full commitment of the supporting personnel which will have to implement it. There is a risk that this implementation may be at the expense of research activities.

Some researchers of the unit are actively supporting and supervising the technology platforms of the unit. This task can sometimes take half of their working time, especially with the rapidly evolving high throughput sequencing technologies and their associated analyses methods. The technical lead of these platforms could be fully delegated to the engineers identified on the organisational chart of the unit.

Assessment of the unit's life and organisation

The unit provides excellent opportunities for researchers of all ages and genders. The unit´s life is well organized and allows vivid exchange of data and ideas.

CRITERION 3: SCIENTIFIC STRATEGY AND PROJECTS

Strengths

Among many other achievements, the unit has essentially contributed to the understanding of the control of body weight regulation via the leptin receptor-MC4R axis. This has paved the way to a more personalized therapy of obese patients carrying a rare mutation in the MC4R. This is proof of principle that the unit follows a successful translational concept of research. A particular strength of the unit is the development of methods which allow the implementation of the concept in clinical practice. Another major strength is the introduction of a human iPSC platform to study the role of mutations in vitro. This was made possible by a strategic recruitment. Part of the work is optimizing and improving methodology which will help maintain international competitiveness. Capitalising on the expertise of teams 1 and 2 and increasing their interaction is another important strategy.

Successfully obtained funding through a "programme d'investissement d'avenir" bid to update genome core laboratory including state of the art DNA/RNA extraction and biobanking, high thoughput genotyping platform, next generation sequencing platforms and bioinformatics and biostatistics – increased productivity and accelerated data generation.

Weaknesses

Hypotheses derived from the genetic results of team 1 could be more stringently incorporated in the project portfolio of team 2.

Assessment of the scientific strategy and projects

The scientific strategy of the unit is excellent and will provide clinically relevant results for personalized therapy of metabolic diseases.

RECOMMENDATIONS TO THE UNIT

A – Recommendations on scientific production and activities (criterion 1)

The scientific production and activities of the unit are outstanding and it is expected that this level will be maintained.

B – Recommendations on the unit's organisation and life (criterion 2)

The interactions between team 1 and team 2 might be further improved to obtain the full potential benefit of the complementary research activities.

The technical lead of the technology platforms of the unit could be fully delegated to engineers.

C – Recommendations on scientific strategy and projects (criterion 3)

Implementation of clinical studies would complete the already excellent research profile of the unit.

RESPONSES TO SPECIFIC QUERIES OF SUPERVISING BODIES

Specific points raised by the Director of CNRS-INSB, in a letter dated 31st January 2019:

Point 1: At present, the unit has no CNRS researchers left and the only CNRS agents occupy missions of engineers and technicians. Therefore, the INSB would like the Hcéres committee to evaluate the relevance for the CNRS to stay as a supervising body for this unit, because of the lack of CNRS researchers and the strong medical connotation/orientation of the projects of the unit.

Evaluation by the committee: the committee noticed that one CNRS researcher is mentioned as co-leader of team 2. However, the committee understands that her administrative affiliation to unit UMR8199 by CNRS is still pending. No other CNRS researcher was mentioned in the staff listing of the unit nor was introduced to the committee.

Research activities at CNRS are generally concerned with fundamental research subjects distinct from medical research subjects. The latter are generally within the remit of Inserm, although it is acknowledged that the limit between fundamental biology and biomedical research is often not sharp, especially in the field of genetics and genomics. Here, the core research activities of the unit are concerned with identifying new genetic variants involved in diabetes, and unravelling the pathophysiological consequences of these mutations at the genomic (i.e. gene regulatory perturbations), cellular or organismal level to facilitate and accelerate the diagnosis of diabetic patients. This will continue in the future, with the inclusion of non-coding mutations (team 1.1 Functional genomics of diabetes), and will be expanded to tighten the link between the genetic perturbation and the specific disease phenotypic spectrum they cause. The research activities of the unit are thus centrally motivated by improving our knowledge of diabetes, not with any fundamental biological process, function, or mechanism. On the other hand, many aspects of genome biology and cellular metabolisms lie on the path from a genetic perturbation to its final pathophysiological consequences, and the unit proposes to investigate some of these, especially as part of the collaboration between team 1 and team 2. The committee therefore concludes that while the unit is chiefly concerned with the biology of diabetes, which is of biomedical interest, it also studies basic biological processes disrupted in the disease.

Point 2: Beside, various CNRS Scientists, Engineers and Technicians have left the unit during the last years invoking a « difficult working atmosphere ». Therefore, the INSB would like the Hcéres committee to check that actions have been taken for the agents/staff and that they can realise their scientific project in serenity.

Evaluation by the committee: the committee held a discussion with the entire technical staff present on that day, i.e. about 40 people, without any group leader present. The technical staff did not report any ongoing issues related to poor working atmosphere. Similarly, the committee held a meeting with 6 out of the 11 scientists listed in the staff chart provided by the unit. The scientists seem to be happy working in the unit and did not report any specific issues. Finally, the committee interviewed separately the two group leaders from team 1 and team 2 and both seemed happy with their current working conditions.

Point 3: Finally, the present director has already conducted many mandates as director since 2002. The CNRS rules in force since 2009 impose that a unit director cannot do more than 2 successive mandates as director of unit in the same unit. Therefore, the present director will not be in a position to assure the direction of the UMR 8199 for the next mandate if the CNRS remains supervising body of this unit.

Evaluation by the committee: the committee feels that this point is outside of the remits of its mission pertaining to the scientific evaluation of the unit.

Point 4: Within its site policy, the INSB will appreciate if the Chairs of the committees and Hcéres scientific advisors in charge of the evaluation of other local units sharing common scientific interests can communicate between them so as to develop in their evaluation reports up to what point the efforts of sharing, collaborations, and interactions between these research units can be enforced to improve the scientific quality and visibility of their activities.

Evaluation by the committee: two other research units located in Lille share similar research interest with unit 8199. These are UMR1011 and UMR1190 directed respectively by Mr Bart Staels and Mr François Pattou and affiliated to Inserm. The three units work in tight collaboration through a joint Labex called EGID. EGID is instrumental for the funding of shared facilities available to all three units. The Hcéres scientific advisor present at the visit of the unit UMR8199 also visited the two other units, UMR1011 and UMR1190 in Lille. He confirms that all three units independently reported at each visiting committee the pivotal importance of the Labex EGID in their individual and collaborative scientific strategies. This is attested by both collective funding grants obtained and common publications. The Labex EGID also positions Lille as a world class scientific site on diabetes.

TEAM-BY-TEAM ANALYSIS

Team 1: Metabolic functional (epi)genomics and their abnormalities in type 2 diabetes and related disorders

Team leader: Ms Amélie BONNEFOND and Mr Philippe FROGUEL

TEAM SCIENTIFIC DOMAIN

Team 1 is dedicated to genetics and epigenetics of diabetes and obesity (and includes Team 1.1. Functional genomics of diabetes). The team develops translational concepts to allow individualized therapies of obese and diabetic patients. It also develops and manages the EquipEx LIGAN-personalized medicine genomic core lab.

TEAM WORKFORCE

	T1	
	Genetics and epigenetics of diabetes and obesity	
Active staff	**Number 30/06/2018**	**Number 01/01/2020**
Full professors and similar positions	4	4
Assistant professors and similar positions	1	4
Full time research directors (Directeurs de recherche) and similar positions	1	1
Full time research associates (Chargés de recherche) and similar positions	1	3
Other scientists ("Conservateurs, cadres scientifiques des EPIC, fondations, industries, etc.")	2	2
High school teachers	0	0
Supporting personnel (ITAs, BIATSSs and others, notably of EPICs)	24	24
Permanent staff	**33**	**38**
Non-permanent professors and associate professors, including emeritus	0	
Non-permanent full time scientists, including emeritus, post-docs	2	
PhD Students	3	
Non-permanent supporting personnel	16	
Non-permanent staff	**21**	
Total	**54**	

CRITERION 1: QUALITY OF SCIENTIFIC OUTPUTS AND ACTIVITIES

A – Scientific outputs and activities, academic collaborations, reputation and appeal

Scientific outputs and activities, academic collaborations, reputation and appeal From 01/01/2013 to 30/06/2018	Genetics and epigenetics of diabetes and obesity
Articles	
Scientific articles	132
Scientific articles with last authorship *(Biology only)*	42
Review articles	11
Other articles (professional journals, etc.)	3
Clinical articles	2
Books	
Scientific book edition	0
Book chapters	3
Meetings	
Meeting abstracts	20
Meetings and congress organisation	11
Electronic tools and products	
Software	0
Databases	0
Tools for decision making	0
Cohorts *(Biology only)*	2
Instruments and methodology	
Prototypes	0
Platforms and observatories	0
Other products	
Artistic creations	1
Movie or theatre play creation	0
Movies	0
Editorial activities	
Participation to journal editorial boards (books, collections)	7
Peer reviewing activities	
Reviewing of journal articles	yes
Grant evaluation (public or charities)	yes

Participation to lab site visit committees (Hcéres, etc.)	yes
Participation to institutional committees and juries (CNRS, Inserm, etc.)	yes
Academic research grants	
European (ERC, H2020, etc.) and international (NSF, JSPS, NIH, World Bank, FAO, etc.) grants	7
National public grants (ANR, PHRC, FUI, INCA, etc.)	14
Local grants (collectivités territoriales)	0
PIA (Labex, Equipex, etc.) grants	2
Grants from foundations and charities (ARC, FMR, FRM, etc.)	16
Visiting senior scientists and post-docs	
Post-docs	6
Visiting senior scientists	1
Scientific recognition	
Prizes	2
Distinctions	0
IUF members	0
Chair of learned and scientific societies	yes
Invitations to meetings and symposia (out of France)	> 50
Members' long-term visits abroad	0

Strengths

This team is among the leading teams in the world addressing the role of gene variants in common metabolic diseases. The team has an excellent reputation and a remarkable network of national and international collaborations. The scientific output is outstanding (*Nat Rev Endocrinol, Nat Genet, Nat Med, Cell Metab*; as lead authors) with one third of these publications as lead authors. The team has attracted 6 post-docs (mostly from abroad) and one visiting fellow during the period. Team members are editorial members of a number of international peer-reviewed journals (e.g. *Cell Metab.; Mol. Metab.*). The fund raising capacity of the team has been impressive (2 ERC > 4 million €; Equipex > 8 M€; Labex EGID > 3.5 M€; FEDER 2.8 M€; RHU > 1.8 M€; ANR > 0.85 M€; etc.).

Weaknesses

None

Assessment of scientific outputs, reputation and appeal

The team has an excellent reputation and a remarkable network of national and international collaborations. The scientific output of team 1 is outstanding.

B – Interactions with the non-academic world, impacts on economy, society, culture or health

Interactions with the non-academic world, impacts on economy, society, culture or health From 01/01/2013 to 30/06/2018	
Socio-economic interactions / Patents	
Invention disclosures	0
Filed patents	1
Accepted patents	0
Licenced patents	0
Socio-economic interactions	
Industrial and R&D contracts	4
Cifre fellowships	1
Creation of labs with private-public partnerships	0
Start-ups	0
Clinical trials *(Biology only)*	0
Expertise	
Consulting	0
Participation in expert committees (ANSES, etc.)	yes
Legal expertise	0
Expert and standardization reports	0
Public outreach	
Radio broadcasts, TV shows, magazines	5
Journal articles, interviews, book edition, videos, etc.	2
Other popularization outputs	no
Debates on science and society	1

Strengths

This team and especially the head of the team is very present in public media promoting disease awareness. They successfully developed very innovative methods (one patent filed). The team got a contract and a Cifre fellowship from Sanofi. The team has filed one patent and one discovery is maturing at present (SATT Nord).

Weaknesses

The team has successfully addressed clinically relevant questions in the past by collaboration with existing cohorts of international collaborators. The low phenotyping quality of existing cohorts often limits the questions which can be addressed in the future. To widen the spectrum of clinical investigations the establishment of clinical trials with deep phenotyping would be desirable.

Assessment of the interactions with the non-academic world

The team is publicly visible and benefits from the scientific reputation of the head of the team for fundraising thereby efficiently supporting translational concepts. The team successfully developed very innovative methods.

C – Involvement in training through research

Involvement in training through research From 01/01/2013 to 30/06/2018	
Educational outputs	
Books	0
E-learning, MOOCs, multimedia lessons, etc.	0
Mean number of publications per student *(Biology & Science and technology only)*	2
Training	
Habilitated (HDR) scientists	6
HDR obtained during the period	1
PhD students	9
Defended PhDs	6
Mean PhD duration	36 months
Internships (BTS, M1, M2)	83
Education	
Courses with international label (ERASMUS, etc.)	0

Strengths

Due to the international visibility of the head of the team, this team is very successful in recruiting promising PhD candidates, visiting fellows and postdocs from all over the world. PhD students generated 2 publications on average, with publications as first authors in outstanding to excellent journals (e.g. (e.g. *Nat Genet; Cell Rep*). Most PhDs have got positions of post-docs (in France and the US) while one became Assistant-Professor and another one research engineer in Lille. The publication record shows that young investigators have excellent opportunities to develop their own scientific carrier thanks to their excellent publications (e.g. *Nat Genet* 2018).

Weaknesses

None

Assessment of the involvement in training through research

The team is attractive for international PhD students, visiting fellows and postdocs. The publication record shows that young investigators have excellent opportunities to develop their own scientific carrier. Thus, the involvement of the team in training through research is excellent.

CRITERION 2: TEAM ORGANISATION AND LIFE

Team organisation and life From 01/01/2013 to 30/06/2018	
Women/men ratio in the team	0.54
Women/men ratio among team scientists	0.8
Women/men ratio among team PhD students	0.4
Women/men ratio among team leaders, team head and deputy heads	0

Strengths

The gender distribution is in the expected range. The scientific exchange in the team is well organized and contributes to the impressive output of the team. Internal seminars dedicated to project progress reports are monthly organized and stimulate the scientific life of the unit.

Weaknesses

This team of 54 people brings together researchers, engineers and technicians around 5 areas of research in very different fields of expertise (from molecular biology to systems biology). Internal communication is mainly in the form of ad hoc project meetings or technology meetings. Team 1 could however benefit from the formal organization of laboratory meetings on a regular basis to catalyse exchanges between projects.

Assessment of the team's life and organisation

The team provides excellent opportunities for researchers of all ages and genders. The scientific exchange in the team is well organized and contributes to the impressive output of the team.

CRITERION 3: SCIENTIFIC STRATEGY AND PROJECTS

Strengths

The genetics platform and methodology are outstanding and will be world leading in the future. If it is accomplished to recruit three new young scientists to Lille, then this would add further expertise to the team. It is impressive how this team in the new proposal is concentrating on the key questions in this field. The approach has the potential to change clinical diagnosis, decisions and therapies based on individual data. In particular the studies of gestational diabetes and chronic kidney disease address the overall questions (i) what explains the diabetes epidemic beyond genetics and adulthood environment (ii) what are the conditions causing the most important diabetes complication. As a new toolbox to achieve these goals, the team has established an iPSC platform. This approach to understand mechanisms in an individualized human cell system is an ambitious, but very promising and innovative approach to delineate the biology behind genetic variants. Substantial amounts of money are already secured (> 4 M€), and many applications (e.g. IHU2; Labex) have been accepted (for a total > 6.5M€) or submitted recently.

Weaknesses

There are no conceptional weaknesses but some of the proposals are based on preliminary, so far unpublished data. This makes it difficult to assess the likelihood of success of these projects. For instance the project characterizing novel GLP-1R agonists with higher and longer glucose stimulated insulin secretion is of high clinical relevance. However, this approach cannot be ultimately assessed without more information about the agonists. Likewise, the effect of GLP-1R agonists on EphB3 receptor activity is very interesting but cannot be fully estimated without more detailed preliminary data. With respect to the phenomic platform no details on phenotypic parameters and clinical methodology are provided. The establishment of a clinical phenotyping platform is a logical consequence of the overall research strategy. In the project on alterations of epigenetic

profiles of long lived CD34+ HSPCs and their involvement in an advanced aging cellular phenotype will be studied. However, the advanced aging cellular phenotype is not defined.

Assessment of the scientific strategy and projects

The team´s scientific strategy and projects are excellent. The projects are scientifically interesting and clinically highly relevant.

RECOMMENDATIONS TO THE TEAM

A – Recommendations on scientific production and activities (criterion 1)

The scientific production and activities of the team are outstanding and it is expected that this level will be maintained.

B – Recommendations on the team's organisation and life (criterion 2)

The team´s organization and life have much improved. No further specific recommendations.

C – Recommendations on scientific strategy and projects (criterion 3)

The scientific strategy and projects are impressive. No specific recommendations.

Team 2: Molecular and cellular pathophysiology of metabolic diseases

Team leader: Mr Jean-Sébastien ANNICOTTE and Ms Régine CHAMBREY

TEAM SCIENTIFIC DOMAIN

The aim of team 2 is modelling of metabolic diseases (obesity and type 2 diabetes, chronic kidney disease).

TEAM WORKFORCE

	T2	
	Molecular basis and modeling of diabetes and obesity	
Active staff	**Number 30/06/2018**	**Number 01/01/2020**
Full professors and similar positions	0	1
Assistant professors and similar positions	0	1
Full time research directors (Directeurs de recherche) and similar positions	0	0
Full time research associates (Chargés de recherche) and similar positions	1	2
Other scientists ("Conservateurs, cadres scientifiques des EPIC, fondations, industries, etc.")	0	0
High school teachers	0	0
Supporting personnel (ITAs, BIATSSs and others, notably of EPICs)	2	3
Permanent staff	**3**	**7**
Non-permanent professors and associate professors, including emeritus	0	
Non-permanent full time scientists, including emeritus, post-docs	1	
PhD Students	1	
Non-permanent supporting personnel	1	
Non-permanent staff	**3**	
Total	**6**	

CRITERION 1: QUALITY OF SCIENTIFIC OUTPUTS AND ACTIVITIES

A – Scientific outputs and activities, academic collaborations, reputation and appeal

Scientific outputs and activities, academic collaborations, reputation and appeal From 01/01/2013 to 30/06/2018	**Molecular basis and modeling of diabetes and obesity**
	Jean-Sébastien ANNICOTTE
Articles	
Scientific articles	12
Scientific articles with last authorship *(Biology only)*	4
Review articles	3
Other articles (professional journals, etc.)	0
Clinical articles	0
Books	
Scientific book edition	0
Book chapters	0
Meetings	
Meeting abstracts	11
Meetings and congress organisation	0
Electronic tools and products	
Software	0
Databases	0
Tools for decision making	0
Cohorts *(Biology only)*	0
Instruments and methodology	
Prototypes	0
Platforms and observatories	0
Editorial activities	
Participation to journal editorial boards (books, collections)	0
Peer reviewing activities	
Reviewing of journal articles	yes
Grant evaluation (public or charities)	yes
Participation to lab site visit committees (Hcéres, etc.)	no
Participation to institutional committees and juries (CNRS, Inserm, etc.)	yes
Academic research grants	

European (ERC, H2020, etc.) and international (NSF, JSPS, NIH, World Bank, FAO, etc.) grants	1
National public grants (ANR, PHRC, FUI, INCA, etc.)	1
Local grants (collectivités territoriales)	0
PIA (Labex, Equipex, etc.) grants	0
Grants from foundations and charities (ARC, FMR, FRM, etc.)	2
Visiting senior scientists and post-docs	
Post-docs	4
Visiting senior scientists	0
Scientific recognition	
Prizes	0
Distinctions	0
IUF members	0
Chair of learned and scientific societies	no
Invitations to meetings and symposia (out of France)	0
Members' long-term visits abroad	0

Strengths

The team has published several high quality papers in collaboration (e.g. *Nat Cell Biol, Cancer Cell; JCI)* or as lead authors (one third*) (e.g. Cell Rep; Mol Metab*). The team got funding from many sources (total > 1.8 Mo €; e.g. ANR, EFSD, grants from Research Strategic Orientations, Diabetes Res. Assoc).

Weaknesses

The number of publications has decreased over the evaluated period, but is expected to increase again upon successful recruitment of further excellent scientists.

Assessment of scientific outputs, reputation and appeal

The publication output appears improvable. It can be expected that the recruitment of further excellent scientists improves the team´s performance with respect to publications.

B – Interactions with the non-academic world, impacts on economy, society, culture or health

Interactions with the non-academic world, impacts on economy, society, culture or health From 01/01/2013 to 30/06/2018	
Socio-economic interactions / Patents	
Invention disclosures	2
Filed patents	1
Accepted patents	1

Licenced patents	0
Socio-economic interactions	
Industrial and R&D contracts	2
Cifre fellowships	0
Creation of labs with private-public partnerships	0
Start-ups	0
Clinical trials *(Biology only)*	0
Expertise	
Consulting	0
Participation in expert committees (ANSES, etc.)	yes
Legal expertise	0
Expert and standardization reports	0
Public outreach	
Radio broadcasts, TV shows, magazines	4
Journal articles, interviews, book edition, videos, etc.	0
Other popularization outputs	no
Debates on science and society	2

Strengths

The team is present in public media promoting disease awareness. The team successfully developed very innovative methods (see patents). The team has been supported by the SATT Nord (> 0.8 M€ for 1 patent and 2 know-how contracts).

Weaknesses

None

Assessment of the interactions with the non-academic world

The team is publicly visible and successful in fundraising and patents. The team´s interactions with the non-academic world are adequate.

C – Involvement in training through research

Involvement in training through research From 01/01/2013 to 30/06/2018	
Educational outputs	
Books	0
E-learning, MOOCs, multimedia lessons, etc.	0

Mean number of publications per student	0
Training	
Habilitated (HDR) scientists	1
HDR obtained during the period	0
PhD students	3
Defended PhDs	2
Mean PhD duration	36 months
Internships (BTS, M1, M2)	18
Education	
Courses with international label (ERASMUS, etc.)	0

Strengths

This team is very successful in recruiting promising PhD candidates, visiting fellows and post-docs from all over the world (e.g. U.K., Belgium, Malta, China). Most PhD grants were from the Ministry of Research and High Education (competitive grants) while one was from the I-Site (Lille University). Mean PhD duration seems to be adequate reflecting international standards. PhD Students displayed publications in high quality journals (e.g. *Sci Rep*) as first authors. Those having defended become post-docs (2 in the US).

Weaknesses

None

Assessment of the involvement in training through research

There is a close interaction of the team members and team leaders guaranteeing a good training through research.

CRITERION 2: TEAM ORGANISATION AND LIFE

Team organisation and life From 01/01/2013 to 30/06/2018	
Women/men ratio in the team	0.3
Women/men ratio among team scientists	0
Women/men ratio among team PhD students	0
Women/men ratio among team leaders, team head and deputy heads	0

Strengths

The team leader is a very integrative personality leading his team in a professional and successful way. The board of reviewers has the impression that the team appreciates the team leader's leadership. The organization in the team seems to be very good. The team meets on every Monday morning for several hours for a data club which ensures strong scientific interaction within the team and allows close and regular access of the team members to the team leader. Internal seminars dedicated to project progress reports are monthly organized and stimulate the scientific life of the team.

Weaknesses

None

Assessment of the team's life and organisation

The team´s life and organisation seem to be excellent.

CRITERION 3: SCIENTIFIC STRATEGY AND PROJECTS

Strengths

The team developed a very valuable toolbox to assess their scientific questions. They follow interesting and novel hypotheses about the contribution of several genes and pathways to the pathogenesis of metabolic phenotypes. They address novel aspects of epigenetic mechanisms such as mRNA methylation in particular the role of Mettl3 and Fto in pancreatic beta-cells. They will develop small molecule drugs to interfere with the histone lysine acetyltransferase Kat2b and to increase glucose stimulated insulin secretion in disease models. Furthermore, the study of the type 2 diabetes relevant gene Cdkn2a in adipocyte browning is important and would be very interesting if the team indeed can show that this mechanism is operative in human tissue as well. Substantial amounts of money are already secured (close to 1 M€), and other applications (e.g. Labex-2) have been accepted (for a total > 0.9 M€) or submitted recently.

Weaknesses

The team follows interesting concepts. The role of specific targets for the development of metabolic disease is dressed in appropriate animal models and *in vitro* systems. The chosen targets are a consequent evolution of the personal scientific history of the team leader. While this makes a lot of sense on one hand it is, on the other hand a missed opportunity not to concentrate also on targets which are defined by the novel results of team 1. It would be a unique potential to study targets which were characterized by team 1. This close combination would be a great advantage for success in the very competitive field of metabolic disease. Team 2 plans to include studies on the pathogenesis of nephropathy and the role of acidosis for the development of insulin resistance. To follow this hypothesis seems to be risky and out of the focus of the team. Even though this is a key question in the field of diabetic complications.

The project exploring the role of transcription factor E2F1 in pancreatic plasticity is intriguing. The team leader has a long history in studying the role of this transcription factor network in the regulation of anabolic and catabolic cellular pathways in different cell types. Now he extends this concept to islet cells. In this context, it would be very important to address the relevance of this molecular network in human material at an earlier stage of the project. It is indeed unclear whether human islet cells show the same plasticity as murine cells.

Assessment of the scientific strategy and projects

The team´s scientific strategy and projects are very good. The projects are scientifically interesting and promising if confirmed in humans.

RECOMMENDATIONS TO THE TEAM

A – Recommendations on scientific production and activities (criterion 1)

The team has published high quality papers, however, the number of publications is not at the level which might be expected from such a team. This should be improved.

B – Recommendations on the team's organisation and life (criterion 2)

None

C – Recommendations on scientific strategy and projects (criterion 3)

Team 2 should build on Team 1's results in a more clear way. It should also check whether human beta-cells function as murine beta-cells very early in their project.

CONDUCT OF THE VISIT

DATE

Start: 5 February 2019 at 08:30

End: 5 February 2019 at 17:30

VISIT SITE

Institution: Faculté de Médecine - Pôle Recherche - Bât EGID

Address: 1 place de verdun, 59045 Lille

CONDUCT OR PROGRAM OF THE VISIT

4 February 2019

Welcome of the expert committee and dinner

5 February 2019

08:30-09:00	Welcome (closed-door): expert committee with the Hcéres Scientific Officer (the role and procedures of Hcéres)
09:00-09:10	Presentation of the evaluation process to the unit by the Hcéres Scientific Officer
09:10-10:00	Presentation of the unit scientific strategy and projects (P. Froguel, director of the unit) (time including 20' for answers to written questions)
10:00-10:40	Presentation of scientific program of Team 1: Genetics and Epigenetics of Diabetes and Obesity (A. Bonnefond/P. Froguel) (20' presentation + 20' discussion)
10:40-11:00	Coffee break
11:00-11:40	Presentation of scientific program of Team 2: Molecular basis and Modeling of Diabetes and Obesity (J.S. Annicotte) (20' presentation + 20' discussion)
11:40-12:00	Debriefing of the expert committee (closed-door)

Discussions and private meetings (in presence of the Hcéres Scientific Officer)

12:00-12:20	Discussion with scientists
12:20-12:40	Discussion with students and post-docs
12:40-13:40	Lunch
13:40-14:10	Discussion with engineers, technicians and administrative personnel
14:10-14:40	Discussion with the representative of the managing bodies
14:40-15:00	Discussion with the director
15:00-17:30	Private meeting of the expert committee (report preparation)
17:30	End of the visit

SUPERVISING BODIES' GENERAL COMMENTS

We will find below either the supervising body's general comments or write:

"Despite the Hcéres' requests, no comments have been received on the day of publication of this evaluation."

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