Récepteurs nucléaires, maladies cardiovasculaires et diabète

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Nuclear receptors, cardiovascular diseases and diabetes

Under the supervision of the following institutions and research bodies:

Université Lille 2 - Droit et Santé

Institut Pasteur de Lille

Institut National de la Santé et de la Recherche Médicale - INSERM

December 2013

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

DEPARTMENT FOR THE EVALUATION OF RESEARCH UNITS

ON BEHALF OF AERES, PURSUANT TO THE DECREE OF 3 NOVEMBER 2006[1]*,*

- MR. Didier HOUSSIN, PRESIDENT
- MR. Pierre GLAUDES, HEAD OF THE EVALUATION OF RESEARCH UNITS DEPARTMENT

ON BEHALF OF THE EXPERT COMMITTEE,

- MR. Laurent LAGROST, 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 assessments contained herein are the expression of an independent and collegial deliberation of the committee.

Unit name:	Nuclear receptors, cardiovascular diseases and diabetes
Unit acronym:	
Label requested:	UMR_S
Present no.:	UMR_S 1011
Name Of Director (2013-2014):	Mr Bart STAELS
Name of Project Leader (2015-2019):	Mr Bart STAELS

Expert committee members

Chair: Mr Laurent LAGROST, University of Bourgogne

Experts:

Mr Yves ARTHUR, University of Bourgogne (Representative of CNU)

Mr Ulrich BLANK, University Paris Diderot

Ms Anne BOULOUMIÉ, University of Toulouse (Representative of INSERM)

Ms Béatrice DESVERGNE, University of Lausanne, Suisse

Mr Jean-Sébastien SYLVESTRE, University Paris Descartes

Scientific delegate representing the AERES:

Mr Jean GIRARD

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

Mr Régis BORDET, University Lille 2

Ms Fabienne JEAN, Institut Pasteur de Lille

Ms Anne ROCHAT, INSERM

Mr Bernard SABLONNIERE (Representative of Doctoral School n°446)

1 • Introduction

History and geographical location of the unit

UMR_S 1011 was created in January 2010, evolving out of unit 545.

UMR_S 1011 is affiliated to IFR142 and IFR114.

UMR_S 1011 is located on 2 distinct sites: Pasteur Institute of Lille and University Campus Lille 2 (in close proximity to the University Hospital)

Management team

The unit is directed by Mr Bart STAELS. He is assisted by a Management Committee composed of team leaders and key persons.

AERES nomenclature

SVE1 LS4

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	5 (2.2)	14 (6.4)
N2: Permanent researchers from Institutions and similar positions	16 (11.2)	15 (10.4)
N3: Other permanent staff (without research duties)	24 (2.5)	32 (26.2)
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	24 (22)	20 (18.5)
N6: Other contractual staff (without research duties)	7 (7)	6 (6)
TOTAL N1 to N6	76 (44.9)	87 (67.5)

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	10	
Theses defended	13	
Postdoctoral students having spent at least 12 months in the unit*	20	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	13	17

2 • Overall assessment of the interdisciplinary unit

Strengths and opportunities related to the context

- strong and recognized expertise of UMR_S 1011 with a first rank, leading position worldwide;

- outstanding track record of unit director and team leaders;

- well-defined research plans with excellent feasibility (in line with previous advances and ongoing workpackages of the unit);

- the unit has access to the necessary platforms and possesses the capacity to develop new technologies. Additional facilities are planned to open by the end of 2015;

- research themes and geographical distribution allow close interactions with strong clinical and surgical departments of the University Hospital and the University, and with strong basic research teams on the Pasteur Institute campus;

- planned access to new laboratory space in 2016;

- several teams (teams 1, 2 and 3) have been joined by clinical researchers and medical doctors allowing further development of well-defined translational projects;

- human resources are anticipated to increase further. The evolving organisation, integration of additional clinicians and planned projects are likely to allow further development of translational Bench to Bedside projects;

- unit is part of the Hospital University Department (DHU) entitled « *Cœur et Vaisseaux : de la Prévention au Traitement, facteurs de risque, cibles métaboliques et pathologie cardiovasculaire* »;

- strong, long-lasting and highly productive partnership with Genfit SA, a biopharmaceutical company which emerged from Inserm U545 and which is engaged in the discovery and development of medical compounds in the therapeutical area of cardiometabolic disease;

- wide collection of transgenic animals in the field with creation of a new animal facility dedicated to metabolic diseases;

- strong collaborations and excellent attractiveness of the unit at the national and international levels;

- unit teams are highly complementary and interact closely;

- significant contribution to the creation and expansion of the European Genomic Institute of Diabetes (EGID), awarded Excellence Laboratory (LabEx) through the national Investment for the Future program;

- excellent interactions of UMR1011 with the local environment (in particular with Federative Research Institutes 114 and 142);

- projects are fully integrated in the Scientific Strategy Policy of the University of Lille 2;

Weaknesses and threats related to the context

- the geographical distribution on two distinct sites requires a strong and effective management;

- highly competitive fields of research with breakthrough technology and experimental design of increasing cost, thus requiring appropriate/elevated funding;

- relatively low number of full-time researchers;

- numerous, highly skilled team members on non-permanent positions;

- loss of full-time permanent INSERM positions (retirements) without replacement in spite of the overall expansion of the unit staff over the last years;

- IFR-driven technical platforms deserve reorganization and reinforcement;

Recommendations

- to maintain and reinforce the current management strategy which allows frequent interactions and complementary competencies on the two sites;

- to finalize expansion of human resources as anticipated;

- to maintain the excellent relationships with social, economical and cultural environment;

- to foster recruitment of young, full-time researchers through national competitive calls (Inserm, CNRS);

- to sustain the emergence of promising, young team leaders;

- to reinforce the permanent administrative staff (in particular through permanent Inserm and University positions);

3 • Detailed assessments

Assessment of scientific quality and outputs

UMR_S 1011 has an international reputation and leadership in studying the physiological function, regulation and pharmacological modulation of nuclear receptors in immune-inflammatory and cardiometabolic diseases. These are complex disorders with inter-organ cross-talk mechanisms that are investigated here in an integrative and comprehensive manner. UMR_S 1011 combines multidisciplinary approaches (including metabolic, immune, inflammatory and vascular insights) that rely on complementary methodological approaches and know-how (including biochemistry, histology, molecular epigenetics, development of genetically-engineered mouse models, metabolic immunophenotyping, cell and whole-body imaging, animal physiology, chemical screening,…). Most of them are accessible through common technical platforms which are in direct and tight link with research projects. Additional external platforms are accessible as core facilities of EGID LabEx, IFR114 and IFR142.

Scope of the research can be summarized as two complementary and well-defined axes: 1) investigation of cellular and molecular mechanisms controlling lipid and glucose metabolism, and 2) development of preventive and therapeutic strategies against dyslipidemia, type 2 diabetes, atherosclerosis and cardiovascular diseases.

UMR_S 1011 involves 4 distinct, but complementary and interacting teams:

- Team 1 'Nuclear receptors in the metabolic syndrome' is devoted to studies of the metabolic functions of nuclear receptors (PPARs, FXR, Rev-erba, RORa) using animal models and human translational research approaches and their interest as potential therapeutic targets in humans ;
- Team 2 'Molecular control of monocyte/macrophage functions in cardiometabolic syndrome' focuses its activities on the role of macrophage subsets in the development of atherosclerosis and their control by PPARs and LXRs. The role of PPARs and LXRs in the molecular regulation of monocyte differentiation and macrophage functions in adipose tissue during obesity is also studied ;
- Team 3 'Nuclear receptors, immuno-inflammation and cardiometabolic diseases' is devoted to studies of the mechanisms by which nuclear receptors control the function of immune cells and their impact on atherosclerosis ;
- Team 4 'Molecular analysis of gene regulation in cardiometabolic diseases' investigates how nuclear receptors control gene expression and affect immune-metabolic functions, aiming at unraveling novel regulatory pathways in order to validate nuclear receptors as pharmacological targets ;

Remarkably, each team develops its research program in close interaction with the others, thus facilitating multidisciplinary and translational approaches. It is highlighted by a number of joint publications (involving authors from two teams or more). In addition, dynamic and productive collaborations have been set up with external technical platforms and with clinical departments, in particular from the EGID LabEx and the University Hospital of Lille.

Past activity of the unit is outstanding. Among the number of advances and breakthroughs of the 2008-2013 period:

- the role of PPARa in non-alcoholic steatohepatitis (NASH) and the development of a novel dual PPARa/d agonist ;
- the role of the nuclear bile acid receptor FXR in the control of lipid and glucose metabolism by bile acids, in particular with consequences on adipocyte differentiation, pancreatic beta-cell function, and glucose homeostasis ;
- the role of Rev-erba in mitochondrial biogenesis, function and autophagy, thus identifying Rev-erba as a possible pharmacological target in some myopathies ;
- the modulation of macrophage phenotype (notably by nuclear receptors or by the tumor suppressor gene P16INK4a) and its consequences on inflammation, atherosclerosis and obesity development ;
- the contribution of adipose tissue macrophages to the development of cancer in obese patients;
- the contribution of PPARa dysregulation to atopic dermatitis ;

- the role of PPARa and –g as negative regulators of IgE-mediated systemic anaphylaxis;
- the contribution of PPARb/d to hepatic fibrosis;
- the implication of PPARa in the resistance to sepsis in mice;
- the control of glycolysis in the liver by FXR and its sensitivity to cellular energy levels;
- the description of novel roles for nuclear receptors in the control of liver and pancreatic b-cell physiology;
- the impact of epigenomic DNA modifications (DNA methylation or hydroxymethylation) on PPARg-driven adipocyte differentiation and induction of TLR4

Scientific production of the 2008-2013 period is outstanding, with 224 publications (including 42 reviews, 2 book chapters and 14 letters or editorials). Eight publications with Impact Factor above 20, 23 with IF ranging between 10 and 20, and 109 with IF between 4 and 10.

Team members show outstanding track record and citation index, including H index of 100 for one member with more than 33000 total citations without self-citations. In a recently published and independent analysis of most cited authors in Europe (*Lab Times*, 2013), one unit member was ranked 4th for the citation number of articles published by european pharmacologists and pharmacists between 2005 and 2011 in *'pharmacology and pharmacy'* journals (as listed by Thomson Reuters' *Web of Science*).

On average, there are 3000 citations per year for publications of all unit members over the 2008-2013 period, with many articles in high-rank, peer-reviewed journals.

Unit members have been invited more than 180 times to national and international conferences as invited speakers.

They have given more than 200 oral or poster presentations in national and international meetings.

Assessment of the unit's academic reputation and appeal

Over the 2008-2013 period, UMR_S 1011 made significant and major contributions 1) to the creation of the European Genomic Institute of Diabetes (EGID) which was awarded an ANR LabEx funding for 8 years, 2) to the creation of the Hospital University Department (DHU) entitled *"Coeur et Vaisseaux : de la Prévention au Traitement, facteurs de risque, cibles métaboliques et pathologie cardiovasculaire"*, 3) to the regional CPER plan axis entitled *"Diabetes and cardiovascular diseases"*, 4) to the attraction and recruitment of new fellows on permanent Inserm or university positions, 5) to a transatlantic network of excellence in cardiovascular disease and therapeutic targets (Leducq Foundation), and 6) to European programs.

UMR_S 1011 has set up and developed numerous scientific collaborations worldwide (USA, The Netherlands, Denmark, Poland, Great Britain, Germany, Belgium, Austria, Switzerland, Portugal, France,…).

Unit members have received a number of national and international prizes and awards, among them Senior member of the *Institut Universitaire de France*, European Lipid Science Award 2010, *"Jean-Paul BINET"* prize 2011 from the Fondation pour la Recherche Médicale (FRM), the 2012 *"Distinguished Leader in Insulin Resistance"* award from the international Committee for Insulin Resistance (ICIR),...

Several members of the research unit are recipients of the Prime d'Excellence Scientifique Inserm and/or Interface Grants.

The research unit has a strong attractiveness for high-standard visiting fellows from many countries and has numerous and productive collaborations worldwide.

During the 2008-2013 period, 22 postdoctoral fellows joined the research unit.

New permanent positions were created, and additional fellows (including 13 clinicians with MCU-PH, PH or PUPH positions) will join teams 1 and 2 of the unit on January 2015.
In 2013, unit UMR_S 1011 organized the COST meeting entitled *"HDL, from biological understanding to clinical exploitation"* and gathering participants from 15 European countries.

The unit director is a member of numerous meeting program committees (Co-Chairman of the Basic Cardiovascular Sciences Conference 2008 (BCVS) – Keystone, CO, USA, July 28-31, 2008; Faculty and Program Committee member of the Annual World Congresses of the Insulin Resistance Syndrome (WCIR); Member of the EAS Program Committee and Advisor to the Executive Committee; Member of the International Advisory Board of the 10th European Symposium on Metabolism – Padua, Italy, October 7-9, 2010; Co-organizer of the 2012 Keystone Symposium on Genetic and Molecular Basis of Obesity and Body Weight Regulation – Santa Fe, New Mexico, USA, January 29 – February 3rd, 2012).

During the 2008-2013 period, the unit has coordinated the scientific animation of the axis *"Diabetes and cardiovascular complications"* of the région Nord Pas de Calais. This axis comprises five labelled units, and covers a large number of laboratories of the Lille 2 University.

During this period, 73 conferences (42 French speakers, 26 speakers from other European countries, 5 non-European speakers) have been organized.

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

The Genfit biotechnology company was co-founded by the unit director who is currently president of the Genfit Scientific Council. The tight partnership of Genfit and UMR_S1001 led to the registration of several patents. Remarkably, recent and ongoing interactions of UMR_S1011 and Genfit led to the development of the GFT505 PPARα/δ agonist which is currently in Phase IIb clinical development for the treatment of non-alcoholic steatohepatitis, a major public health concern. UMR_S1011 has also set up a strong collaboration with UMR761 for drug discovery with planed patent registrations.

Several members of UMR_S1011 take a significant part in research administration and evaluation at a local, national and international level (including head of the ethics committee for animal experimentation of the Nord-Pas de Calais Region, AERES delegate and members of AERES evaluation committees, elected members of Inserm and university Scientific Councils, members of learned societies, members of medical training/education councils,…)

UMR_S1011 is integrated in the *"Nutrition-Santé-Longévité"* competitiveness cluster of the Nord-Pas de Calais region.

With respect to cultural interaction with the environment, the unit participates actively in the *"Pasteur kid Campus"* and INSERM *"Destination Labo"* initiatives, which allow children from primary and secondary schools to get in touch with research. The unit also contributes annually to the *"Fête de la Science"* event, as well as to the *"Salon de l'étudiant et de l'étudiant santé"*, the *"Salon des grandes études et de la recherche"* and the *"Salon des Masters"*.

Members of UMR_S1011 deliver general public conferences (e.g. *"Pasteur 5 à 7 meetings"*) which target a non-specialist adult audience.

Communication to the general public is also made through the internet web site of the research unit (http://www.u1011.lille.inserm.fr), a video with general information on unit activities, conference presentations to local industrial partners at the *"Pépite Lille Metropôle Innovation"* meeting, and several interviews published in local or national newspapers (i.e. Le Monde, 9 mars 2013).

Assessment of the unit's organisation and life

The organisational flow chart of UMR_S1011, as provided, is functional and well-defined, with 4 research teams and 1 administrative and logistical team.

Briefly, the statutory unit Council (unit director, financial officer, persons in charge of the Pasteur Institute and CHRU sites, team leaders, elected members) meets twice a year, with a General Assembly once a year.

The Scientific Council of UMR_S1011 is common to the EGID Scientific Council as part of the PIA LabEx program.

A Management Committee of the unit (composed of the unit director, team leaders and key persons) meets on a weekly basis. It is the operative part for the daily management of the unit. It interacts with external institutions and makes strategic choices.

Scientific coordination is made through project follow-up meetings (on a weekly basis, including students/post-docs and team leader), thematic group meetings (every 2-3 weeks, including project members and team leader), and a steering committee (every 6 weeks, including project members and unit director).

Finally, research teams are supported by a logistical and administrative staffs, which ensures interactions with institutions (Inserm, Université de Lille2 and Institut Pasteur de Lille). This staff contributes also to grant applications and management (interactions with Région Nord-Pas de Calais, Europe, ANR,…), financial management, laboratory safety, scientific animation, communication, etc…

Besides providing technical know-how and support to the other teams of the unit, each team is also interacting and collaborating with teams outside the unit, in particular by giving access to their platforms. Even though priority is given to the unit's research projects, the platforms are open to other teams (mostly, but not exclusively in Lille) yielding several productive collaborations through specific technological competences (including for instance laser micro-dissection, histology, and immunophenotyping). When appropriate, technicians and engineers appear as co-authors on scientific publications.

Internal scientific animation of the unit is remarkable with seminars by invited national and international collaborators, organization of internal "unit meetings", "journal club", one annual EGID "Think tank" (one full day of presentation of Egid projects), and oral or poster presentation of research data during seminars.

Impressively, unit UMR_S1011 has made a highly significant contribution to creation and upgrading of a number of technical platforms. Organization of and access to technical platforms, whether they are internal, common/shared, or external is exemplary. A brief overview of technical platforms is provided below:

- Internal platforms:

Biochemistry platform: it allows measurement of classical range of biochemical parameters (glucose, lipids, transaminases ...) and is required for proper mouse phenotyping. It allows fruitful academic and industrial collaborations.

Histology platform: it has been recently completed with a laser capture microdissection station. This device allows the isolation and study of the properties, distribution and functions of cells from the arterial wall and metabolic tissues that are obtained from human clinical studies or genetically-modified murine models.

Epigenetic platform: a microarray station is used to analyze mRNA and miRNA expression profiles in cellular models, primary cells and tissues of various origins. An evolutive bioinformatic pipeline has been implemented and is routinely used to process and analyse new generation sequencing data.

- Common/shared platforms:

Access is given within the EGID framework, and within the framework of the ANR Labex and the Region Nord Pas de Calais.

Metabolic immunophenotyping: The metabolic immunophenotyping platform is expected to open during the first semester of 2014. It will allow to explore further the complex link between changes in immune cell populations/functions and metabolic alterations.

Animal facility and metabolic platform: a new animal facility is currently built up on the hospital campus. It comes in addition to the animal facilities at Pasteur Institute and will include new paradigms dedicated to metabolic phenotyping.

Whole body imaging: UMR_S 1011 has access to Computed Tomography for whole-body scanning of mice. This equipment has been set up in the High technology IMPRT-IFR114 Animal Facilities on the hospital campus and is made accessible to other researchers.

Exploration of cardiovascular function: invasive and non-invasive measurements of cardiovascular functions (blood pressure, heart rate…) in genetically-modified and dietary manipulated animal models are currently upgraded. These measurements are relevant to all experimental animal protocols used in the unit.

- **External platforms:**

Members of UMR_S 1011 have access to the cell and animal imaging, microarray and proteomic analysis platforms of the "Institut de Médecine Prédictive et Thérapeutique" IMPRT/IFR114 and the Pasteur Institute/IFR142. UMR_S 1011 also benefits from numerous academic, industrial and clinical collaborations with several (inter)national groups and through industrial and European consortiums. Transversal collaborations within the Prime axis (supported by the région Nord Pas de Calais) allow drug development using a screening platform to identify new chemical entities which regulate genes of interest in metabolic and cardiovascular diseases.

Assessment of the unit's involvement in training through research

A number of members of UMR_S1011 are teachers at the faculties of pharmacy and medicine of University Lille 2 (14 full and associate professors). Unit members are actively involved in the Master "Biologie-Santé" of the University of Lille 2 for both academic and laboratory training. The unit hosts many trainees (Master 1 and 2, BTS technical degree, PhD students). Several members of the academic research staff (other than teachers) of the unit also teach in the Master school or continuous educational programs (i.e. animal experimentation training).

PhD Students (not exceeding 1.5 PhD students per thesis supervisor) follow a compulsory doctoral training organized by the doctoral school. Students are asked to present in English and on a regular basis their results during the unit's meetings. The scientific communication and interactions between students are facilitated through a weekly journal club in English which gathers all the PhD as well as Master students and post-doctoral fellows. They are encouraged to actively present their results in national (NSFA, Symposium ALFEDIAM, …) and international meetings (EVGN, ELC Tützing, EMBO conferences, Cell Signalling meetings, Summer School on Nuclear Receptors, AHA,...). At the end of the PhD training period, each student has taken part in at least one meeting. PhD students benefit from a compulsory annual follow-up meeting with external advisors. The unit hosted Erasmus students from Italy, Poland and Turkey. Overall, unit members significantly contribute to organisation and management of the doctoral school (*Conseil de l'École Doctorale, Comités de suivi de thèses, jury de concours pour l'attribution des allocations doctorales*).

Once a year, and starting from 2014, an internal mini-congress will be organised within EGID, with all the features of an international congress (including call for abstracts managed by an external selection committee). Posters and oral sessions will give students the opportunity to improve their presentation skills. The teaching project of the unit is actually tightly linked to the EGID student training project, as part of the local Master Program Biology-Health. From 2010, novel courses have been introduced at the M1 and, more intensively, the M2 levels, with "thematic days" dedicated to themes directly connected to scientific research of the unit. On this basis, a course/speciality entitled *"Diabetes, obesity and cardiometabolic complications"* has emerged within the Master Program. It has been formalised in 2013 and will be effective from 2014. This master will allow attracting students in the field of cardiometabolic diseases and might evolve towards an Erasmus Mundus Master.

The first EGID summer school has taken place in September 2013. It was open to PhD students, post-doctoral students and engineers from European laboratories. This Summer school will be renewed every 2 years.

Since 2008, 13 students from the unit defended their PhD thesis, and among them 8 are currently post-doctoral fellows in France or abroad. One PhD student now holds a researcher position in France (at University), and another one is working in a Biotechnology company.

Since 2008, 5 competencies for research direction (HDR) have been defended by young researchers or teachers from UMR_S 1011 and 3 are scheduled in the near future. Today, 13 researchers of the unit hold HDR.

Assessment of the strategy and the five-year plan

Research plans, very well defined, are in direct link with the 2008-2013 fruitful past activities.

For the next 5-year period, UMR_S 1011 will pursue the investigation of the molecular and biological mechanisms involved in dyslipidemia and type 2 diabetes and their cardiovascular complications. Special interest will be given to specific nuclear receptors with the aim to identify new targets or treatment strategies to correct the defective pathways.

Undoubtly, UMR_S 1011 possess the know-how, and has access to all required molecular tools and technological equipment (cellular and molecular biology, biochemistry, histology, animal experimentation, animal models, immuno-phenotyping, EGID animal facility).

Beyond the administrative organization in 4 teams, the global strategy of the unit is remarkable and consists of a transdisciplinary, translational approach focusing on 3 transversal topics associating nuclear receptors and cardio-metabolic diseases: 1) Fatty acids and PPARs, 2) Bile acids and FXR, and 3) Circadian rhythms and RORα-Reverbα.

UMR_S 1011 is one of the three founder units of EGID. This new institute (supported by Inserm, CNRS, CHRU Lille, University Lille 2, Institut Pasteur de Lille, Lille Communauté Urbaine, région Nord-Pas de Calais as institutional and/or financial partners) is expected to expand by 2020. UMR_S 1011 will remain a major contributor to the development of the EGID Labex project.

Several grants will continue beyond 2015 (EuRhythDia, Chronotherapeutic lifestyle intervention for diabetes and obesity to reset the circadian rhythm and improve cardio metabolic risk in the European working population). The Leducq Network is running until the end of 2015, and the RESOLVE project until 2017. Several funding applications are continuously submitted by members of the unit.

Of course, UMR_S 1011 will pursue numerous collaborations with local, national or international laboratories.

In order to reinforce research on cardiovascular diseases in Lille, and to increase interaction with CHU de Lille, the Unit is actively involved in the creation of a DHU (Département Hospitalo-Universitaire – *"Cœur et Vaisseaux : de la Prévention au Traitement, facteurs de risque, cibles métaboliques et pathologie cardiovasculaire"*). The DHU project is in the development phase, but has already gained principle of agreement of the key participants and of Université Lille 2 and the CHRU Lille.

4 • Team-by-team analysis

Team 1 : Nuclear Receptors in the Metabolic Syndrome

Name of team leader: Mr Bart STAELS

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	2 (1)	4 (2)
N2: Permanent EPST or EPIC researchers and similar positions	7 (4.2)	7 (3.9)
N3: Other permanent staff ~~(~~without research duties~~)~~	4	6 (5.2)
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	6 (5.5)	7 (6.5)
N6: Other contractual staff (without research duties)	2	2
TOTAL N1 to N6	21 (16.7)	26 (19.6)

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit*	8	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	4	5

• Detailed assessments

Assessment of scientific quality and outputs

During the 2008-2013 period, the various team members have contributed to 143 publications (57 with 1 team member as first and/or (co-)last author) including 113 original publications. The list of publications of this group is impressive and of very high impact (Nature Medicine, Hepatology, Gastroenterology, J Clin Invest) demonstrating the ability of the team to produce high-ranking research with several highly referenced papers in the field. They published numerous articles in journals with an impact factor > 9. The team has a very strong international reputation for its research. In summary, this team has reached a very high level of scientific quality and expertise in the field. The publication output is outstanding and the impact of the group is major in all the domains covered.

Assessment of the unit's academic reputation and appeal

- recruitments: A young researcher with teaching duties joined team 1 in 2010. In addition to 5 post-doctoral fellows (of whom 4 have left Team 1 since 2010), 4 post-doctoral fellows were further recruited;

- edition: Team leader is/was an editorial board member of several journals and contributed to/co-edited the International Union of Basic and Clinical Pharmacology (IUPHAR) Compendium of Nuclear Receptors;

- expertise: team members perform scientific expertise for (inter)national institutions and funding agencies; international journals and scientific committees;

- invitations: Team leader (137 invited lectures) and members of Team 1 are regularly invited to national and international meetings;

- coordination and public funding: Team 1 is/was coordinator of different projects (FRM-P16 (2007-2010), FCA-PPARs (2006-2009), CPER-DIABETE (2007-2009), CPER-REGUCLOCK (2008-2010), CPER-PRIM, ANR-FXREN). Team leader is coordinator of the 'cardiometabolism' axis of the 2007-2013 CPER project and is co-founder of LABEX ANR EGID;

- participation to other public funded projects: Team 1 is/was participant in numerous (inter)national funded projects (EU projects HEPADIP LSHM-CT-2005-018734 (2005-2010), X-TRA-NET (-2008), TOBI (2008-2010), STIGO (2007-2011), COST Actions BM0602 (-2011) and BM0904 (2010-2014), EuRhythDia (2011-2016), DIAMAP (Road Map for Diabetes Research in Europe FP7 200701), FUI – BETADIAB (2009-2011), AMIDIAB (2006-2009), OSEO – OLNORME (2007-2009), Fondation LEDUCQ (2010-2015), EU FP7 RESOLVE, IT-Diab,…);

- prizes: Team leader has received the European Lipid Science Award 2010, Munich; the "Jean-Paul BINET" prize 2011 from the Fondation pour la Recherche Médicale, Paris; and the 2012 "Distinguished Leader in Insulin Resistance" award from the International Committee for Insulin Resistance (ICIR), Los Angeles;

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

Team 1 has/had several contracts with pharmaceutical, biotechnology (Genfit) and nutrition industries. Several patents have been registered. Of note, continuing collaborations exist between Team 1 and Genfit yielding one compound currently in Phase IIb clinical development. Team 1 participates in several private-public consortia (IT-Diab, AMIDIAB, OSEO-Olnorme, FUI-BETADIAB). The biochemistry platform participates in fruitful academic and industrial collaborations thanks to its mouse phenotyping expertise. The team leader is co-coordinator of the European Genomics Institute of Diabetes (Labex) and Diabetes from Metabolic syndrome to Cardiovascular complications of the 7th CPER.

Assessment of the unit's organisation and life

The team is composed of a substantial number of researchers, engineers and students. On January 2015, the team will be composed of 1 researcher, 4 MCU, 4 PU and 1 MCU-PH, 6 engineers and 2 assistant-engineers. Three researchers with teaching duties and 1 academic clinician will join the team because of complementary expertise and previous collaborations. Team organization is founded on different subgroups with specific projects.

Assessment of the unit's involvement in training through research

Team 1 is affiliated to the PhD program ED446 Biologie-Santé, Lille, and the Master Biologie-Santé (M1 Lille 2, M2 Lille 1-Lille 2). Most of the team members have high teaching duties. Three members of Team 1 have a HDR in 2013. In 2015, Team 1 will have 5 members with HDR. During 2008-2013, Team 1 has formed 6 Master 2 and 6 PhD theses were defended. Presently, 1 Master 2 and 3 PhD training programs are on-going. No information is currently available on the follow-up of doctoral students in link with doctoral schools and the care taken with the integration of doctors into the job market.

Assessment of the strategy and the five-year plan

The overall objective of the team is to decipher the molecular and cellular impact of nuclear receptor, such as PPARs, FXR and Rev-erb/ROR, in the metabolic homeostasis. Three main projects will be developed during the next five years: i) NASH, Metabolic Syndrome and PPARs, ii) Bile Acids, FXR and the Metabolic Syndrome, and iii) Circadian Rhythm, Metabolic Syndrome and Rev-erb/ROR. These projects rely on the internationally recognized expertise of the different team members and may lead to major breakthrough in the field. All the projects are based on the development of sophisticated experimental models of genetically modified mice. Of great interest, at least two projects (project i and project ii) have strong translational aspects including the use of human samples and identification of synthetic compounds that may have therapeutic applications. In this line, the team has already screened and identified synthetic compounds acting on TGR5 (patents registered; project 2). Overall, the project of team 1 is an excellent, high standard, serious and well-conceived research project based on excellent preliminary results and a long-standing experience in the field. It is a translational project that runs from basic science to clinical investigation. This project may lead to the identification of potential gene networks and biomarkers associated with metabolic diseases.

Conclusion

- **Strengths and opportunities:**

Already long history of excellent track record (many publications of very high quality)

International reputation

Appropriate current funding level

High quality of the proposed project

- **Weaknesses and threats:**

No weakness intrinsic to the scientific capability and organization of the team.

- **Recommendations:**

The team leader is encouraged in his long-term policy to support the development of young staff members as independent researcher.

The team should aim at attracting at least 1 permanent position from Inserm.

Team 2 :

Molecular control of monocyte / macrophage functions in cardiometabolic syndrome

Name of team leader:

Ms Giulia CHINETTI

Workforce

Team workforce	Number as at 30/06/2013[1]	Number as at 01/01/2015[2]
N1: Permanent professors and similar positions	2 (1)	9 (4.2)
N2: Permanent EPST or EPIC researchers and similar positions	3 (2.5)	2
N3: Other permanent staff (without research duties)	5 (4.8)	10 (5.05)
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	7 (6.5)	5
N6: Other contractual staff (without research duties)	2	1
TOTAL N1 to N6	19 (16.8)	27 (17.25)

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit*	6	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	7

• Detailed assessments

Assessment of scientific quality and outputs

The research activity of the team is well focused on the study of monocyte/macrophage populations in atherosclerosis and obesity with a specific emphasis on the role of the molecular pathways involving the nuclear receptors PPARγ and LXRs. The main results highlight the role of PPARγ and LXR pathways in the heterogeneity of the macrophage populations within human atherosclerotic plaque (in terms of cell surface markers associated with metabolic and phagocytotic functions). The comparative study between human adipose tissue and tumour associated macrophages reveals unexpected similarities. The approaches have been mainly performed on human samples (native cells obtained after immunoselection, laser-captured materials or in vitro differentiated cells) re-inforcing the patho-physiological relevance of the observations. An additional original research axis has been developed and concerns the role of the cyclin-CDK inhibitor CDKN2A $p16^{INK4a}$ (p16), a key regulator involved in age-related diseases and in monocyte/macrophage polarization. The approaches performed on murine models (mouse $p16^{INK4a}$ deficiency, mice transplanted with p16(-/-) bone marrow) and on ATM, MDM and human blood monocytes allowed to decipher the role of p16 in macrophage polarization and its consequence on atherosclerosis development, obesity, and glucose intolerance.

Local and international collaborations have been set up on several axes (PBMC and ATM from obese subjects; TAM; CD68(+) (MR)(+) M2 macrophages in human atherosclerotic plaques).

The results obtained are original and published in the best journals of the field. Since 2008, the team has produced 51 original articles (12 with IF>9, 22 with IF>5) including 17 directly from the group (Blood 2011, Diabetologia 2011, Circ Res. 2011, 2013, J. Biol. Chem 2012, Arterioscler. Thromb. Vasc. Biol. 2012) and 35 in collaboration and 16 reviews. Twenty-eight publications are collaborations with team 1, 3 and/or 4. They are regularly presented at major national and international meetings in the field.

Assessment of the unit's academic reputation and appeal

The team has national and international regognized expertise in the field of nuclear receptors in inflammation in vascular and metabolic diseases as shown by 19 invitations in lab seminars and congress (national and international).

The team was involved in the coordination of national projects: FRM, 2011-2014; Fondation de France, 2011-2014; ANR “AIMHA”, 2010-2013; CPER “ChoMetAlt” 2008-2010.

Members of the team have been recipients of an Inserm Interface Contract (2008-2013), “Prime d’excellence scientifique” (PES) from Inserm (2011-2014) and from the Université de Lille 2 (2012-2016).

Members of the team are experts for the Ministère délégué à l’Enseignement Supérieur et à la Recherche « partenariat Hubert Curien » project, for « conseil régional de la région Nord Pas de Calais », and for AERES.

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

Members of the team participate in collaborative contracts with Genfit SA and ImaBiotech (France), Bicoll (Germany): OLNORME Eurotrans-bio project: « Occurrence of novel Ligands for Nuclear Orphan Receptors in plant metabolites » (2007-2010), Servier (since 2002), Roche (2010-2011), Friesland Foods corporate research (since 2008). One Patent is mentioned (Provisional-US. Application N°: 60/999,119. Filing date: 16/10/2007).

The team has a high capacity to get financial support (since 2008 1 640 355 €) at the local (University), regional and national (ANR, FRM), european (participant EU project TOBI (2008-2011) and international (participant in the Fondation Leducq Transatlantic network of Excellence -"High-density lipoprotein dysfunction in the development of cardiovascular disease and as a therapeutic target” (2010-2014)) levels.

The team is involved in “Fête de la science”.

Assessment of the unit's organisation and life

In June 2013, the team is composed of 5 researchers, 3 PhD students, 4 post-doctoral fellows and 5 permanent and 2 non-permanent technicians. Starting from 2015, members of the EA2693 team of the University of Lille 2 will join Team 2.

Assessment of the unit's involvement in training through research

The team is affiliated to the doctoral school 446 (Biologie et santé)

The team has 3 HDR, and 4 PhD theses have been trained since 2010, 3 are in progress and one is scheduled late 2013.

The team is actively involved in the Labex EGID training project, as part of the Master Biologie-Santé of Lille (novel courses M1 and M2 level, with “thematic days”), coordinates an ERASMUS exchange program with the University of Padova (Italy), Faculty of Pharmacy.

Three post-docs were in the team and 4 are currently trained by the team; one post-doc has been recruited as MCU at the University of Lille 2. Visiting students (Italy, Austria) are mentioned.

Assessment of the strategy and the five-year plan

The proposed project is in the line with the past activities (characterization of macrophage subsets in human atherosclerotic lesions, impact of obesity on monocyte phenotype) with additional interesting and original axes including the contribution of macrophages and their subtypes to vascular calcification in atherosclerosis with the study of calcium phosphate homeostasis in macrophage sub-populations and the impact of PPARγ target genes in the trans-differentiation of macrophages to osteoblasts and/or osteoclast. Preliminary results as mentioned support the working hypotheses.

Another new research axis is proposed and concerns the early phase of the fibro-calcific process of aortic valves and more specifically the involvement of interstitial cells. This new axis is original, based on expertise of the clinicians joining the team and may open original and interesting research area.

The proposed approaches are broad, ranging from the « omics » (including transcriptomic (with mirRNAs), proteomic analyses of LCM-isolated macrophage, and mass spectrometry imaging (MSI) technology) to histological atherosclerotic plaque sections, in order to establish a signature of human macrophage subtypes.

The project is original and based on the technical know-how and expertise of the team. Some new approaches will be performed in collaboration and the feasibility is sustained by the ongoing collaborations with clinicians and benefits from a very good financial support.

Conclusion

- **Strengths and opportunities:**

Recognized expertise in the field of nuclear receptors in inflammation and in vascular and metabolic diseases

Broad approaches from mouse models to human biopsies with emphasis on native cells (laser-captured cells)

Established collaborations with clinicians and many interactions with the other teams

Development of an original and interesting research axis on fibrocalcification process of aortic valves

- **Weaknesses and threats:**

The research projects may remain descriptive in its preliminary phase

- **Recommendations:**

The committee recommends to maintain the research focus on the involvement of nuclear receptors in macrophages in vascular and metabolic pathologies and to continue to develop mechanistic and integrative approaches.

Team 3 : Nuclear receptors, immuno-inflammation and cardiometabolic diseases

Name of team leader: Mr David DOMBROWICZ

Workforce

TEAM WORKFORCE	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1 (0.2)	1 (0.2)
N2: Permanent EPST or EPIC researchers and similar positions	2 (1.5)	2 (1.5)
N3: Other permanent staff (without research duties)	2	3
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4 (3.5)	3 (2.5)
N6: Other contractual staff (without research duties)	2	2
TOTAL N1 to N6	11 (9.2)	11 (9.2)

TEAM WORKFORCE	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	3	
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	2	2

• Detailed assessments

Assessment of scientific quality and outputs

The team "Nuclear receptors, immune-inflammation and cardiometabolic diseases" headed by David DOMBROWICZ has been created in 2010 when he moved from Inserm U547. During the current term, the team leader gradually adapted the project of immune-inflammatory studies in allergy (where the team has a proven track record of excellence) to the study of immune-inflammation in metabolic diseases. Many of the achievements of the 2008-2013 evaluation period still relate to the work initiated in Inserm U547, but the transition phase is well underway.

Since 2010, the team has been able to increase in size with 4 persons hired under permanent contracts including 1 researcher with teaching duties (MCU), 1 academic clinician and 2 technicians. The team has also recruited several new post-doctoral fellows. Since 2008, the team has published 67 research papers consisting of 49 original publications with about 1/3 (16) directly emanating from the team, and the others corresponding to collaborations (either with the other teams of the unit or with outside research groups). The publications are of good quality some of them with an impact factor close to 10 (2 JACI, Blood). Most of the other publications from the group are in journals relating to their specialty. Some of the collaborative work has been published in very high impact factor journals (2 Nat Med). Team members have also written 18 reviews witnessing the recognition in their field.

Assessment of the unit's academic reputation and appeal

The team is a well established, nationally and internationally recognized research group in the field of allergic immuno-inflammatory studies. Its reputation in the new field of research cannot be judged due to the fact that this change occurred very recently. Members of the team have coordination responsibilities both in National (ANR, PHRC) and international grants (EU Cost) and the team leader has important editorial tasks in different journals (Ass. Editor J. Immunol, Int. Arch All.& Immunol), as well as in evaluation bodies (AERES). Over the years, the team has built a large number of both national and international collaborations that have led to common publications. The attractiveness of the team leader is also underlined by many (15) invitations to International meeting (Japanese Society of Allergology), as well as good success in obtaining funding. The team has obtained international contracts for collaborations with industry and several ongoing contracts. Some of them capitalize on the recent switch in thematics, partly based on the unique expertise of the team on the analysis of immune cell functions. The switch to the field of metabolic research, now largely underway after the transitional phase, undoubtedly represents a new opportunity on which the team can capitalize.

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

Although the team abandons somewhat its traditional field, the team leader has made a strategical decision to develop a new research axis. Examination of the role of immune cells in cardiometabolic disease now provides an opportunity for interdisciplinary research. The team's unique and outstanding expertise in the analysis of immune-inflammation is highly integrative, thus favouring collaborations with other team members. It has led to obtaining collaborative grants with industry (OSEO Micropath). The team offers strategic specific expertise for the setup of animal models as testified by the team leader position as the president of the Ethics Committee for Animal Experimentation Nord - Pas de Calais (CEEA75) since 2009. The team is highly engaged in the planning of the new animal facility that will be housed in a new building. The presence of an academic clinician favours translational research in the original field of dermato-allergy, which is now connected to the vasculo-metabolic field. The team, based on its unique expertise within the EGID labex represents also an essential driving force for the establishment of the new metabolic immuno-phenotyping platform. Finally, the team can be viewed as a highly integrative driving force both at the unit, but also at the Nord- Pas de Calais regional level.

Assessment of the unit's organisation and life

During the first term within the unit, the team has incorporated well into the unit activities. The project is highly integrative and collaborations with other team members are favoured in a highly efficient manner as testified by the many common publications with other teams of the unit. Members of team 3 have taken on important responsibilities, notably the establishment of an immunophenotyping platform useful for all unit members. The team leader is highly engaged in getting the animal platform going. Indeed, the visiting committee could appreciate that other permanent staff members recognize the valuable expertise of the team leader in the management of animal studies. By restructuring the group, the team leader allowed the emergence of a new synergy in a novel interdisciplinary research area. The team has been able to grow and set up a coherent organisation strategy THAT capitalizes both on the experimental animal interface but also on the opportunity to engage clinically related translational research.

Assessment of the unit's involvement in training through research

Team 3 is affiliated to the PhD program ED446 Biologie-Santé, Lille. The team leader is currently co-supervising a PhD student studying the involvement of innate lymphoid cells in obesity-induced asthma. As team leader in Inserm U547, during the 2008-2009 period, he (co)supervised 3 PhD thesis, which were successfully defended: Role of PPARα in atopic dermatitis, Role of IgE and IgG receptors in atopic dermatitis, Eosinophils and innate immunity: expression and role of TCR$\gamma\delta$ in anti-tumoral defense. The team has also supervised 1 Erasmus Master (University Perugia, Italy, 2011) on the expression of FXR in T lymphocytes and has hosted another Erasmus fellow (Jagellonian University Krakow, Poland) for a 3 month summer visit to work on the regulation of MCP-1-Induced Protein/Regnase-1 by PPARα. The team has supervised 4 local master (M2R) students during the period (Expression of TCR$\alpha\beta$ by mouse eosinophils, 2008; Role of CX_3CR1 in lymphocyte polarization in atopic dermatitis, 2009; Is TReP-132, a nuclear receptor co-factor, involved in smooth muscle cell proliferation ?, 2010; Psoriasis and metabolism: a pathohysiological link, 2012).

Assessment of the strategy and the five-year plan

The five-year plan clearly indicates that the transitional phase of the first term is terminated with all projects being now clearly oriented towards the general theme of the unit, and allowing efficient collaboration within the unit. One project will examine the pathophysiological link between psoriasis and metabolism based on a number of indications in the literature that there could be a connection. This connection will be investigated both in animal models of psoriasis and clinical studies building on a cohort of patients (Psoriasis/ Atopic Dermatitis) distinguished by their metabolic phenotype. Preliminary results indicating changes in glucidic metabolism and insulin signalling have already been obtained. The second project examines the relationship between bile acids, immune cell metabolism and energy homeostasis. It is based on experimental animal studies in which bile acid responsive elements such as the TGR5 cell surface receptor and the FXR nuclear receptor will be examined after specific knock-down in immune cell population using Cre technology based on primary expression analysis. Initial results have already been obtained, notably in B cells. The third project examines the immune regulatory mechanisms operative in adipose tissue inflammation and metabolic dysfunction, again based on specific knock-down of nuclear receptors in identified immune cell populations. This project is also associated with the regional excellence cluster EGID LabEx benefiting of a cohort of diabetic and non-diabetic morbidly obese patients undergoing bariatric surgery. It indicates the full integration of the team in the general scientific policy of the unit. The projects show that the team has an unique expertise in analysing immune cell phenotypes and function. It opens up a new promising research axis both at the level of the unit and within the North Pas-de Calais region. The projects are consistent, original and ambitious. They represent a balanced mix of studies in animal models and studies in patient cohorts based on the expertise of the team leader and the clinical associated service. All projects are funded. They are feasible as preliminary results have been obtained, but, given the still relatively small size of the team, it is possible that some reflection to cut-back on some aspects may be necessary unless additional personnel is recruited.

Conclusion

The team has a good publication record and during the first term has managed to shift from immunoinflammation in allergy models to immunoinflammation in vasculo-metabolic models. This additional effort, in continuation of the earliest projects of team, should be welcomed. It clearly represents an asset for the unit, providing a new dimension of research to the field of immuno-inflammatory investigation. The new project is ambitious involving a good mixture between animal studies and patient investigations and is based on the complementary expertise of team members. The team takes on important responsibilities both at the unit and regional level.

- **Strengths and opportunities:**

The team has high level of expertise in the analysis of immunoinflammation, now being applied to a new topic with considerably interdisciplinary potential. The team represents a driving force for development of a state-of-the-art platform on metabolic immunophenotyping both for animal studies and investigations in humans. The interdisciplinary approach of the new project provides clearly an asset on which the team can capitalize. Experimental animal studies will be helped by the newly developed animal platform conceived under the supervision of the team leader. The clinical studies are based on cohorts available in the associated clinical services and integration in the labex EGID excellence cluster

- **Weaknesses and threats:**

Three large scale projects are presented for a relatively small team. Although during the visit, the team leader clarified the individual responsibilities (involving experienced post-docs, but on a contractory basis), the threat remains that projects, which involve high level of animal breeding strategies cannot be completely secured due to the small size of the team.

- **Recommendations:**

Recruitment of a permanent researcher (EPST) should be envisaged. The team leader bears enormous administrative responsibilities some of which he should consider to abandon.

Team 4 : Molecular analysis of gene regulation in cardiometabolic diseases

Name of team leader: Mr Philippe LEFEBVRE

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	4 (3)	4 (3)
N3: Other permanent staff (without research duties)	3	3
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	7 (6.5)	5 (4.5)
N6: Other contractual staff (without research duties)	1	1
TOTAL N1 to N6	15 (13.5)	13 (11.5)

TEAM WORKFORCE	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended		
Postdoctoral students having spent at least 12 months in the unit*	4	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

Team 4 focuses on the molecular mechanisms involving members of the Nuclear Receptors superfamily, in the context of metabolism and inflammation in cardiometabolic diseases. As such, team 4 has the specificity in the unit of carrying the most updated molecular approaches, with a clear aim in understanding molecular mechanisms. With that respect, all projects that are developed within team 4 are carefully selected for their coherence with the projects performed in other teams.

The productivity of team 4, created in 2010, is presently taking a very dynamic shape. A total of 37 papers, of which 21 correspond to the ongoing projects started in 2010. Beside an important JCI paper in 2010, the production in 2011 and 2012 can be considerate as moderate in terms of impact. However, the team can present for 2013 an outstanding performance by publishing in a high impact generalist journal (JCI) and in the best of the specialty (Hepatology) as well as three other papers. There is no doubt that this reflects an excellent emerging scientific production.

Being in charge of a crucial platform for molecular approaches is also a demanding task that must be recognized as it serves the whole unit and beyond.

Assessment of the unit's academic reputation and appeal

The members of team 4 are well-known in the field of nuclear receptors, albeit the number of invitations remained modest (4 invitations). The high quality of the 2013 publications is likely to give a much better visibility of the team.

The team is involved in coordinating or contributing to one FP7 and three ANR projects. It also clearly contributes to the local and regional efforts in coordinating research platforms.

The team could recently attract one CNRS staff researcher, 2 post-doc fellows and 2 technicians. Team members are solicited as reviewers for funding agencies (French and European) and for international peer-reviewed journals.

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

Team 4 has an important role in teaching, particularly in the pharmacy school, and contributed to the establishment of a professional title (licence, DEUST) in “Health and environment”.

In parallel, members of team 4 obtained and managed grants from the pharmaceutical industry, totaling 1.1.M€. They also participate to fund-raising committee in the context of EGID.

Sensitization of a broad public to science carriers is proposed through participation of the team to various forums.

Assessment of the unit's organisation and life

In 2013, the team is composed of 2 full-time researchers, two assistant professors, and 4 engineers, 3 post-doctoral fellows and 4 PhD students. Altogether, this composition is well equilibrated. Internal meetings as well as meeting across the full unit allow regular presentation and discussion of the various projects, ensuring that integration and appropriate collaboration take place.

Assessment of the unit's involvement in training through research

Team 4 is affiliated to the Doctoral School ED446. Over the last 5 years, they have been supervising 9 master students and 8 PhD students. Given the size of the team, this is a very good contribution to research training.

Assessment of the strategy and the five-year plan

As stated above, the goal of team 4 is on the one hand to maintain and further develop a high quality expertise in NR-related molecular mechanisms, particularly those requiring unbiased approaches, and on the other hand to pursue specific projects anchored in the recent and novel observations of the team.

Along with the latter line, one project will pursue the characterization of FXR post-translational modifications, more specifically its phosphorylation status, and its interactome. A second project, centred on the role of PPARα in NASH will benefit of a PPARα mutant, recently created by the team, that allows dissociation of the DNA binding-dependent activities from others.

Along the former line, one project will develop the tools to assess the epigenomic events regulating nuclear receptor function in adipocyte differentiation. This will be complemented by approaches allowing the study of long intergenic non-coding RNAs. Finally the bio-informatic support will be further reinforced to meet the requirements of the projects of the team and those of the whole unit.

Altogether, these projects are original and ambitious. The proposed techniques are well mastered and will be efficiently updated, in part through collaborations. There is an excellent integration of each project within the themes developed by the unit. The feasibility is very reasonable.

Conclusion

Team 4 was created de novo in 2010. In this short period of time, the committee considers that the team has achieved the expectations that were pointed at the time of the creation: bringing a high quality expertise in new methods for analysing molecular mechanisms, and integrating the general themes covered by the unit, both in terms of project designs but also in terms of making the team being really a part of the unit, regardless the geographical distribution.

Albeit the visibility of this team remains to be improved, the scientific records are showing very high dynamism.

- **Strengths and opportunities:**
  - High levels of competence in new technologies
  - Ambitious and original projects allying epigenomics and genetics
  - Key role for the whole unit in helping projects from each team to further mechanistic approaches

- **Weaknesses and threats:**
  - International visibility needs to improve
  - Helping various projects in the unit may disperse the efforts of the team

- **Recommendations:**
  - The good integration of the projects with those of the entire unit must not have a dispersive effect for the team 4. Cohesion of the projects within team 4 must also be a priority.
  - This may mean that, if the team does not grow, a tightening of the themes may be needed.
  - The excellent bioinformatic expertise should be secured

5 • Conduct of the visit

Visit date:	Thursday, December 12, 2013
Start:	Thursday, December 12, 2013, at 8:00 am
End:	Thursday, December 12, 2013, at 4:30 pm

Visit sites:	Institut Pasteur de Lille
Institution:	Inserm, Institut Pasteur, Université Lille 2, EGID
Address:	1 rue du professeur Calmette - BP245 – 59019 Lille – France

Second site:	Faculté de Médecine-Pôle recherche-Bât. J&K
Institution:	Inserm, Institut Pasteur, Université Lille 2, EGID
Address:	Boulevard du Professeur Jules Leclercq - 59045 Lille Cedex – France

Conduct or programme of visit:

MORNING (LOCATION: PASTEUR INSTITUTE OF LILLE)

• 8.00-8.30 am	Briefing with committee members and AERES scientific delegate (closed doors)
• 8.30-8.45 am	Meeting with representative of the university of Lille2
• 8.45-9.00 am	Meeting with the unit director
• 9.00-9.30 am	General presentation by the unit director (including questions and answers)
• 9.30-11. 50 am	Scientific presentations by team leaders (including questions and answers)
• 11.50-12.20 am	Discussion and former evaluation by committee members with the AERES scientific delegate (closed doors)
• 12.20-12.40 am	Meeting with institutional representatives

Afternoon (location: University of Lille 2 – Medicine Faculty – J&K building)

• 2.00-2.30 pm	Concomitant meetings with representative of PhD Students/Post-docs, Technicians/Engineers, and Researchers/Teaching Researchers,
• 2.30-4.45 pm	Meeting of committee members with the AERES scientific delegate (closed doors)

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 13 mars 2014

V/Réf. : E2015-EV-0593560Z-S2PUR150007721-006647-RT

Objet : Observations de portée générale sur le rapport d'évaluation de l'unité *Nuclear receptors, cardiovascular diseases and diabetes*

Monsieur le Directeur,

Considérant le rapport que vous m'avez récemment transmis, je vous remercie au nom de l'Université Lille 2 et en particulier du directeur et des membres de l'unité *Nuclear receptors, cardiovascular diseases and diabetes,* pour la qualité de l'évaluation effectuée le 12 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).

Le Directeur de l'unité n'a aucune observation de portée générale ni remarque à apporter sur le rapport d'évaluation.

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

Pr. Xavier VANDENDRIESSCHE