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

Department for the evaluation of research units

AERES report on unit:

Inflammation: regulation, interaction with nutrition, and therapeutic innovation

Under the supervision of the following institutions and research bodies:

Université Lille 2 – Droit et Santé

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

December 2013

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

Department for the evaluation of research units

On behalf of AERES, pursuant to the Decree of 3 november 2006[1]*,*

- Mr. Didier HOUSSIN, president
- Mr. Pierre GLAUDES, head of the evaluation of research units department

On behalf of the expert committee,

- Ms. Nadine CERF-BENSUSSAN, 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:	Inflammation: regulation, interaction with nutrition, and therapeutic innovation
Unit acronym:	LIRIC
Label requested:	UMR_S
Present no.:	Fusion UMR_S995, EA 2686, EA 2694, EA 2693, EA 4481, EA 4484
Name of Director (2013-2014):	Mr Pierre DESREUMAUX (UMR_S995), Mr Lionel PRIN (EA 2686), Ms Brigitte JUDE (EA 2693), Mr Alain DUHAMEL (EA 2694), Ms Patricia MELNYK (EA 4481), Mr Rémi NEVIERE (EA 4484)
Name of Project Leader (2015-2019):	Mr Pierre DESREUMAUX

Expert committee members

Chair:	Ms Nadine CERF-BENSUSSAN, INSERM, Paris
Experts:	Mr Juan IOVANNA, Inserm Marseille (representative of CSS INSERM)
	Mr Alf LAMPRECHT, Université de Franche-Comté, Besançon
	Ms Ebbe LANGHOLZ, University of Copenhagen, Denmark
	Mr Philippe MARTEAU, Université Paris 7 (representative of CNU)
	Mr Renato MONTEIRO, INSERM, Paris
	Mr Emmanuel MOYSE, Université de Tours
	Mr Bernard PIPY, INSERM, Toulouse

Scientific delegate representing the AERES:

Mr Joost VAN MEERWIJK

Representatives of the unit's supervising institutions and bodies:

Mr Régis BORDET, Université Lille 2

Mr Samir OULD ALI, INSERM

Mr Bernard SABLONNIERE (representative of Doctoral School "Biology, Health" N°446, Lille)

1 • Introduction

History and geographical location of the unit

• HISTORY

A research team on Inflammatory Bowel Disease headed by Mr Pierre DESREUMAUX was first created in 2001 by INSERM and Université Lille 2 and was the nucleus of a larger unit (INSERM U 995 « Inflammation: Regulation and interactions with nutrition and candidosis ») created 2010 and also headed by Mr Pierre DESREUMAUX. This unit included three other teams; "Glycan interface host-candida" (heads: Mr Daniel POULAIN and Mr Thierry JOUAULT), "Inflammatory diseases with eosinophilia" (head: Ms Monique CAPRON), and "Nutritional modulation of inflammation and infection" (head: Mr Frédéric GOTTRAND).

The new LIRIC center « Inflammatory digestive diseases: pathophysiology and therapeutic targets development » headed by Mr Pierre DESREUMAUX will comprise seven teams resulting from the restructuration of U 995 and merge and restructuration of five previously independent university (EA) teams.

Team 1: U 995 teams 1 and 3 merge into novel team entitled, "Inflammatory digestive diseases: pathophysiology and new therapeutic targets development", which will be headed by Mr Laurent DUBUQUOY, CR1 Inserm. It integrates one biomathematician CR1 Inserm from an AVENIR team shared with Bichat, Paris.

Team 2: Former U 995 team 2, "Fungal-associated invasive and inflammatory diseases" will now be headed by Mr Boualem SENDID, PUPH Parasitology, Mycology.

Team 3: A novel team, "Immunity, inflammation and fibrosis in auto- and allo-reactivity", will be headed by Mr Patrick VERMERSCH, PUPH in Neurology; this team is former EA 2686 directed from 2010 to 2013 by Mr Lionel PRIN, PUPH in Immunology.

Team 4: Former U 995 team 4, "Nutritional modulation of inflammation and infection", will be headed by Mr Frédéric GOTTRAND, PUPH in Pediatrics.

Team 5: A novel team, spin off of U 995 team 1, "IBD and environmental risk factors: from epidemiology to functional analyses », will be headed by Ms Corinne GOWER-ROUSSEAU, PH (from former EA 2694).

Team 6: A novel team "Glycation: from inflammation to aging" results from the merger of EA 2693 "Vascular Aging Biology Group" (Ms Brigitte JUDE, PUPH) and EA 4484, "Cell death signals, mitochondrial metabolism and myocardial dysfunction" (Mr Rémi NEVIÈRE, PUPH). It will be headed by Mr Eric BOULANGER, PUPH.

Team 7: A novel team "Therapeutic innovation targeting inflammation" merges chemists from two university teams and from the engineer school HEI (Hautes Études de l'Ingénieur) (EA 4481 "Groupe de recherche interdisciplinaire innovation et optimisation thérapeutique" and "Impact de l'environnement chimique sur la Santé") and will be headed by Mr Philippe CHAVATTE, PU.

• GEOGRAPHY

U 995 is presently located in the research building of the Medical Faculty of Lille.

Members of the novel center are currently scattered on five sites of the campus and in the "École des Hautes Études d'Ingénieur" (HEI). Teams 1-6 will be gathered during 2014 on two floors of the research building presently hosting U995. For security reasons, chemists will remain located in a distinct university building and at the HEI (20 minutes by subway) in new and adequately equipped laboratories.

U 995 is integrated in and benefits from the platforms of IFR 114 and of the future SFR platforms. It plans to be part of an SFR "Inflammation and Immunity" with the center led by Mr Camille LOCHT at Institut Pasteur Lille with which demands of funding will be submitted to the Région Nord Pas-de-Calais.

Management team

The leader of the project, Mr Pierre DESREUMAUX, has already shown his remarkable dynamism and expertise in federating local research forces and establishing a strong network with regional economical forces.

The executive board will comprise the head of the center, the team leaders, and a newly recruited INSERM scientist dedicated to laboratory management (issued from the local Inserm DR). The administrative board will include all "umbrella organisms" (INSERM, university, CHRU, Regional Council NPC, Engineer School HEI). The need for a scientific board has been expressed but this still needs to be organized.

AERES nomenclature

SVE1_LS7: Epidemiology, public health, clinical research, biomedical technologies

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	42	50
N2: Permanent researchers from Institutions and similar positions	4	5
N3: Other permanent staff (without research duties)	27	28
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	4	3
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	10	12
N6: Other contractual staff (without research duties)	9	11
TOTAL N1 to N6	**96**	**109**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	23	
Theses defended	41	
Postdoctoral students having spent at least 12 months in the unit*	13	
Number of Research Supervisor Qualifications (HDR) taken	28	
Qualified research supervisors (with an HDR) or similar positions	45	45

2 • Overall assessment of the unit

The unit performs excellent translational research based on large cohorts of adult and paediatric patients (IBD, liver diseases, multiple sclerosis, eosinophilia, fungal diseases, cystic fibrosis, renal and bone marrow transplantation). It has contributed substantially to national and international therapeutic trials, notably in IBD, alcoholic hepatitis (U 995), multiple Sclerosis (future team 3), published in high impact journals. Important contributions were also realized in Epidemiology based on EPIMAD, the largest register for IBD in the world. Through collaborations between U995 and future team 7, therapeutic anti-inflammatory compounds were developed. The unit has an excellent visibility in the field of IBD, Hepatology, Multiple sclerosis, and Nutrition and demonstrates a remarkable integration in regional social and economical networks with notably a start up, numerous and multiple industrial collaborations and important responsibilities of the unit members in Université Lille 2. The novel LIRIC project, which will gather 7 teams derived from the 4 teams of U 995 and of several research teams issued from the CHU or from HEI, represents a novel step to structure local research around inflammation with three objectives:

1) identification of physiological factors driving inflammatory diseases;

2) identification of biomarkers;

3) development of new therapeutic formulations and targets.

The project is led by a very dynamic and expert leader and is strongly supported by the Université Lille 2.

Strengths and opportunities related to the context

Strong forces in clinical research based on very large cohorts of patients with a spectrum of inflammatory or immune mediated disorders and strong experience in epidemiology and clinical trials.

Strong interface with chemists experts in drug design.

Strong activity of valorisation with opportunities deriving from identification of several potential therapeutic targets, the inclusion of a team of chemists with expertise in drug design, the presence of the biotech able to test candidate molecules in animal models, many industrial collaborations and expertise in clinical trials.

A very dynamic, insightful and federative leader able to drive and foster interactions between the teams of the center as well as between academic and non-academic partners of the center.

Strong will of the different teams to combine expertise and develop interactive projects with already effective and efficient interactions.

Strong support from Université Lille 2 to federate a large center around the theme of inflammation with regional visibility.

Weaknesses and threats related to the context

Risks arise from:

1) the very large spectrum of diseases with distinct pathophysiological mechanisms which may cause dispersion on many distinct pathways and targets inasmuch as there is;

2) a disequilibrium between a large staff of members with clinical or teaching duties and only four full time researchers with the risk to limit in depth mechanistic approaches and therefore the impact of “mechanistic” publications, important to foster academic recognition.

Recommendations

Promote the recruitment of (an) experienced full-time scientist(s) able to strengthen mechanistic approaches.

3 • Detailed assessments

Assessment of scientific quality and outputs

Indication is given that U 995 has published over 500 papers during the past four years, 40 % with an impact factor (IF) > 5 and 72 (>30 %) published by a member of U995 positioned in first or last author. The unit's members have given 100 invited conferences. A total of over 1000 articles and 20 patents is indicated for all teams together. Members of the unit gather the highest SIGAPS scores of Lille CHRU.

The unit performs excellent translational research based on large cohorts of adult and paediatric patients (IBD, liver diseases, multiple sclerosis, eosinophilia, fungal diseases, cystic fibrosis, renal and bone marrow transplantation).

It has contributed substantially to national and international therapeutic trials, notably in IBD, alcoholic hepatitis (U 995), multiple Sclerosis (future team 3), published in high impact journals. Overall, members of the unit indicate that they have participated to 58 trials, 30 % of which driven by the unit. Two trials published in NEJM and Gastroenterology are directly issued from U 995. One on-going phase 2 clinical trial is based on collaborative work within U 995 on fungal colonisation of the Crohn's disease mucosa.

Important contributions were realized in Epidemiology based notably based on EPIMAD, the largest register for IBD in the world with over 23000 included patients and articles published in Gastroenterology (2008, 2011), Gut (2013), Am J Gastro, IBD, DGL, Aliment Pharm Ther. The unit's members have used mouse models of colitis to demonstrate a proinflammatory role of aluminium, suggested by epidemiological studies (Mucosal Immunology 2013). Another important contribution consisted in the building of a European cohort of 3500 adolescents (Helena) to analyse their nutritional status.

Through collaborations between U995 and future team 7, therapeutic anti-inflammatory compounds, which are based on targets defined by previous work of the teams (PPARγ and CB2 receptor agonists without psychotropic effects, a Schistosoma derived compound), were developed. Of note, the unit presently carries out a phase II assay with a drug company to test a potent PPARγ agonist lacking cardiovascular side effects.

Teams of the future center performed mechanistic studies on the role of NOD receptors as a modulator of neutrophil migration to liver (Gastroenterology 2010), on the mesenteric fat as a source of inflammatory mediators (Gut 2012), on the role of smoke in the activation of anti-inflammatory T/NK cells (PlosOne 2013) (U 995, team 1), on pro- and anti-inflammatory effects of *C. albicans* glycans (JBC 2012 and PlosOne 2012), and on the role of mucus or polyunsaturated fatty acids in cystic fibrosis (in progress in team 4).

Overall, this work represents excellent translational research in keeping with the considerable preponderance of very active clinicians among the staff. Interesting results concerning a spectrum of mechanisms participating in inflammation in intestine, liver, and lung, were obtained.

Assessment of the unit's academic reputation and appeal

The unit has an excellent visibility in the field of IBD, Hepatology, Multiple sclerosis, and Nutrition, which is attested by a large number of invited conferences, UEGW prize 2009 to a member of team 1, L'Oreal/Unesco for women prize 2009 for a member of team 7, the participation to many clinical trials, the writing of guidelines for diseases (Cystic fibrosis, Alcoholic hepatitis). It has a well-recognized expertise in the field of mycology and mannan/glucan biology.

The unit participates importantly to the assessment of national (AERES, ANR) and international (NIH) grant-applications. Its members have an important review activity for major specialty and general journals.

The research projects proposed by the unit's members have yielded numerous national (ANR, PHRC, Aviesan), European (FP7), and international (NIH) grants.

The unit's members have important responsibilities at local, regional, national (INSERM, ANR, Health Ministry), and European (ESPGHAN, ECCO committees, report for European Parliament) levels. The vice-president of Université Lille 2, the Associate-Dean of the Medical Faculty, the vice-president for International affairs (leader team 6), and the chairman of the Biomedical Research Committee (leader team 4), are members of the center.

Unit's members have organized several congresses, workshops, or sessions of meetings in IBD, Hepatology, Nutrition, and Medicinal Chemistry, via the DigestScience Foundation and through links with Societies at the national, European, and international levels.

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

The experts committee appreciated a remarkable integration in regional social and economical networks with notably :

1) a startup (Intestinal Biotech Development, with 3 % royalties to Université Lille 2;

2) a Charity Foundation, DigestScience, created and headed by the head of the center, is funded through partnerships with industry, and organizes different meetings for the general public;

3) the managed care network INTESTINFO, regrouping all gastroenterologists of the North of France;

4) a very active network of GI physicians to implement the EPIMAD register for IBD.

The center's members have filed 20 patents and have multiple industrial collaborations among which three projects funded by the local "Société d'accélération de transfert de technologie".

The center participates to a phase II assay led by a drug company on a PPARγ agonist identified through collaboration between teams 1 and 7.

Members of team 4 chair important national and European committees for Nutrition, notably at AFSAP and EFSA, and have written guidelines for cystic fibrosis. A member of team 7 has been expert for the French and the European Parliament for cannabis use.

Assessment of the unit's organisation and life

The experts committee observed a remarkable effort to structure local research around inflammation with three objectives:

1) identification of physiological factors driving inflammatory diseases;

2) identification of biomarkers;

3) development of new therapeutic formulations and targets.

All teams indicate their adhesion to these three objectives.

This effort is strongly supported by the university, which is willing to provide space to host all teams (currently scattered on the campus) in the same research building (except for the chemists who, for security reasons, will remain in dedicated laboratories on the campus or in HEI). The university is also willing to help with human forces (in 2015 one new MCU-PH in Gastroenterology and an Engineer-technician will be recruited).

Equipment and models handled by the different teams are or will be shared. Large equipment (such as Imaging) will be accessible through the SFR platforms. Funding requests for equipment in sequencing (for microbiota analysis, not yet available) is planned.

Regular meetings within the teams or gathering all teams are already organized and considered as functioning satisfactorily in U 995. They will be extended to the center.

Plans are made to reinforce human forces with notably an MCU-PH (MD PhD) for team 1 and the likely attraction of an experienced INSERM CR1 for team 3.

Assessment of the unit's involvement in training through research

All teams belong to the Doctoral School ED 446 Biology-Health of the Université Lille 2. Since 2008, a total of 46 PhD theses were defended. All graduated PhD students have several publications. The center's teams also hosted numerous Master year 2, Master year 1, and BTS (technician school) students for their internships. Students' follow-up is ensured though regular meetings with their advisors and by internal seminars.

The center's members teach at different levels at the Université Lille 2 and Engineer Schools, including a spectrum of Master 2 courses. Team 1 contributes to the organisation of an international diploma (DIU on inflammatory bowel diseases; team 6 organizes a national master on aging; team 7 a Master in drug design.

Assessment of the strategy and the five-year plan

There is a remarkable effort by a determined and charismatic leader to federate local forces around inflammation supported with enthusiasm by the concerned teams and by the founding research-bodies, notably the Université Lille 2. Objectives are centered around bench-to-bedside approaches with a strong will to identify therapeutic targets, to design corresponding targeting drugs, and to rapidly translate these results to the clinic. To achieve this challenging objective, the team leaders and notably the head of the center have developed a strategy based on strong interactions with chemists that are experts in drug design and on cooperation with industry resulting in an exceptional integration in the socio-economical environment.

There is a risk of scientific dispersion given the large number of themes and pathologies to be studied, but interactions are already obvious between the groups and clear objectives and projects to foster interactions have been indicated (already demonstrated during the past contract gathering four teams).

All projects seem largely funded by a combination of institutional and private grants (even if all teams express anxiety for decreased funding in their SWOT analysis).

The experts committee noted disequilibrium between part-time researchers (over 90 %, mainly of clinical training) and full-time researchers who may be needed to invest in innovative basic approaches and foster mechanistic studies. The strong support of the "umbrella institutions" and of the Region and recent possibility of funding via a Charity foundation provide opportunities to attract talented scientists.

Overall the strategy and five-year-strategy appear very good and best suited to foster the development of innovative clinical research in the field of inflammation in Lille.

4 • Team-by-team analysis

Team 1: Inflammatory digestive diseases: pathophysiology and new therapeutic targets development

Name of team leader: Mr Laurent DUBUQUOY

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	15	15
N2: Permanent EPST or EPIC researchers and similar positions	2	3
N3: Other permanent staff (without research duties)	4	5
N4: Other professors (PREM, ECC, etc.)	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	5	4
N6: Other contractual staff (without research duties)	4	2
TOTAL N1 to N6	**31**	**30**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	9	
Theses defended	11	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken	9	
Qualified research supervisors (with an HDR) or similar positions	10	10

• Detailed assessments

Assessment of scientific quality and outputs

Teams 1 and 3 of the U 995 will merge to novel team 1. Listed production for teams 1 and 3 includes 265 original articles, 93 reviews, 10 patents, 8 book chapters and 215 published abstracts.

In general, the production highlights remarkable forces in translational activities to define and test therapeutic targets or protocols in inflammatory bowel diseases (IBD) and liver diseases. The considerable list of publications also reflects an extensive network of collaborations for clinical trials. The experimental and preclinical work (approximately 15 articles) is published in good or very good journals. Several therapeutic proposals or trials have been published in outstanding journals (e.g. NEJM).

Significant contributions directly implemented by teams 1 and 3 have been made along three axes:

1) A major well recognized IBD axis:

- in epidemiology: analysis of world's largest cohort of IBD (EPIMAD > 23 000 patients) with articles in e.g. Gastroenterology, Gut, and IBD delineating characteristics of IBD in children and elderly and involvement of environmental factors. Demonstration of the aggravating effect of aluminium in mouse models of intestinal inflammation (Mucosal Immunology). This activity leads to the spin off a novel team in the future center (see novel team 5);

- pursuit of the characterisation of the anti-inflammatory and anti-carcinogenic effects of PPARγ (Carcinogenesis, Exp dermatology) Development of a potent PPARγ agonist lacking toxic effects and of novel cannabinoid receptor agonists in collaboration with future team 7 and a drug company with an on-going Phase II trial in ulcerative colitis;

- original demonstration that the mesenteric fat is a source of CRP in response to bacterial translocation in human and experimental IBD (Gut);

- realisation of the first trial in IBD using regulatory T cells with a phase 1/2a assay using OVA specific regulatory T cells in 29 patients affected with Crohn's disease and resistant or intolerant to other therapies (Gastroenterology).

2) A second, more recent, gut-liver axis:

- interesting results on the role of NOD receptors in the recruitment of polymorphonuclear cells in liver (Gastroenterology) and on the smoke in improving experimental (DSS-induced) colitis by a mechanism implicating NKT cells (PlosOne);

- results on the interest of early liver transplantation in alcoholic hepatitis (NEJM 2012) leading to a research project funded by NIH in June 2013.

3) Analysis of anti-inflammatory effect of the Schistosoma-derived enzyme P28GST in experimental models of IBD and in an clinical phase II trial (work in progress).

Assessment of the team's academic reputation and appeal

The team has an excellent academic reputation in the field of IBD (one member was awarded the UEGF Prize 2009 and hired in New York) and of hepatology, with several remarkable publications and an important lecture (Leon Schiff lecture, Boston).

They have given 30 invited conferences, 235 presentations and posters, which indicates the team's excellent visibility.

The two former teams participate to the assessments of national (AERES, ANR) and international (NIH) grant-applications and has an important review-activity for major specialty and general journals.

The teams have obtained substantial national (ANR, INCA, CPER) and international (NIH) grants.

Members of the two former teams have important responsibilities at the local, regional, and national level (e.g. INSERM, ANR). Team 1's leader is head of the ECCO committee for research grants in IBD. Former team 3's leader is Vice President of the Université Lille 2. Team 1's leader has made remarkable efforts to structure Lille research on digestive inflammation resulting in the new project of a research center.

Organisation of conferences, notably in Lille in 2012 (lymphatics and adipose tissue in IBD) and in Vienna in 2013 (intestinal fibrosis).

93 reviews published since 2008, mainly on therapeutics or clinical aspects of IBD or liver diseases, including: one in Lancet, two in Nature Rev Gastroenterol, three in Gut, one in NEJM, and one in J Hepatol.

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

This is a major and impressive strength of the team. It has filed ten patents and has numerous industrial collaborations, notably for drug development (providing 30 % of the budget). The team obtained funding from a Biotech created by team 1 leader. It offers mouse models of intestinal inflammation to test drugs to private companies. Four clinical trials have been or are being performed under the direct leadership of the team.

The "Foundation DigestScience" created in 2008 by the leader of former team 1 promotes strong partnership between clinical and research teams and between local public and economic actors and attracts large and durable funding. This foundation has selected and provided grants to European teams of excellence until 2013. This budget will become available for sponsoring novel research projects or teams within the future center.

The team has remarkable collaborations with the regional network of GI physicians to :

1) build the EPIMAD register;

2) organize courses for IBD diagnosis and management. It also has strong interactions with patients' associations.

Assessment of the team's organisation and life

The organization of former teams 1 and 3 relied on a staff mainly composed of university academics (HU) with only very few full-time scientists. It appears, however, coherent and efficient. Regular meetings, e.g. journal clubs, are held with students.

There is a remarkable effort of scientific structuration, which leads to the emergence of a new leader for novel team 1; of a new, innovative, and successful theme of research in hepatology; and of the spin-off of a novel team on epidemiology.

Assessment of the team's involvement in training through research

The former teams 1 and 3 supervised 20 PhD students, 11 of which graduated since 2008, and 16 Master year 2-students. They supervised 5 MD theses that concerned the analysis of EPIMAD data. The teams organized regular meetings with students, e.g. journal clubs. The future careers of PhD students were facilitated by their predominant origin from the Faculties of Medicine or Pharmacy.

Several members of the two former teams participate to teaching in Master degree, to juries of the Doctoral School "Biology, Health" and to a national online course on IBD organized by GETAID.

Assessment of the strategy and the five-year plan

The novel team 1 of the new center on digestive inflammation results from the merger of U 995 team 1 without the Epidemiology part (which spins off as a novel team), U 995 team 3, and one CR1 staff-scientist from an Avenir team of mathematicians shared with the site of Bichat in Paris. The new leader, a full-time scientist, has a long term collaboration with a previous team leader (who will become head of the center) and has developed strong partnership with the teams' hepatologists.

As in the past, the team pursues a Bed-to-Bench strategy taking advantage of strong interactions with clinicians with the general goal to develop novel therapeutic tools. It will follow-up on-going work on a new PPARγ nuclear target, on the development of clinical strategies using NKT cells, on P28GST for IBD treatment, on NOD1 antagonists to prevent liver ischemia reperfusion (in collaboration notably with team 7). A new original project based on data obtained by the new team leader and the hepatologists and funded by NIH concerns alcohol-induced liver pathology. Two potentially very interesting axes have been defined concerning alterations in liver regeneration and mechanism of susceptibility to infections in patients with cirrhosis. It also develops a very interesting project of mathematical modelling to assess procedures of diagnosis and of patient-management in hepatology. All projects are already largely funded and seem feasible. They are well integrated in the general objectives of the new center. Overall the strategy and five-year plan seem very good.

Conclusion

- **Strengths and opportunities:**

Strong forces in Gastroenterology and Hepatology with clinicians highly motivated and implicated in research and with access to well-characterized and large cohorts of patients and human collections of tissues providing opportunities for excellent and original bed-side to bench research.

Excellent interactions between members of the team. Remarkable interactions with industry providing opportunities for translating results of research in therapeutic tools and for efficient economical valorisation.

- **Weaknesses and threats:**

Net disequilibrium between a large staff of members with heavy clinical duties and only two full time researchers with the risk to limit in depth mechanistic approaches and therefore the impact of “mechanistic” publications, important to foster academic recognition.

- **Recommendations:**

To strengthen mechanistic approaches and bring them to the level of translational research would further foster scientific recognition.

Team 2: Fungal associated inflammatory and invasive diseases

Name of team leader: Mr Boualem SENDID

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	2
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)	4	3
N4: Other professors (PREM, ECC, etc.)	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1
N6: Other contractual staff (without research duties)	1	
TOTAL N1 to N6	**9**	**8**

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

• Detailed assessments

Assessment of scientific quality and outputs

Listed production of this team, which works on Candida and candidiasis, includes 43 original articles (including approximately 22 articles directly emerging from the team), 8 reviews, 4 patents, 2 book chapters, 52 oral communications, 27 posters, and 20 international conferences on invitations, overall attesting a very good scientific output.

Publications, citations, and invited conferences reflect expertise in the molecular organization and regulation of the cell wall mannan and glucan biosynthesis in Candida spp and their relation to pathogenicity. Experimental work of the team (approximately 10 articles) and medical mycology (12 articles) are published in good to very good journals in the field. Six articles in collaboration with team 1 analyse the contribution of fungal infection to Crohn's disease. Two publications, also in collaboration with team 1, study the modulation of intestinal inflammation by yeasts and cell wall extracts.

Significant results directly implemented by team 2 concern:

1) the role of cell wall structural organization in fungal proliferation and host immune recognition and notably the role(s) of mannans in innate immune recognition. This work led to propose fungal mannans as diagnosis markers for invasive candidiasis (J. Biol.Chem; Glycobiology);

2) the role of fungal cell wall components in the immune modulation of macrophages (J. Biol. Chem.);

3) the demonstration that Candida albicans can promote chronic inflammation through galectin-3 in experimental mouse models of colitis (J. Infect. Dis.);

4) in collaboration with team 1, the analysis, in dextran sulphate sodium-induced colitis, of beneficial or adverse effects of yeasts and their glycan components depending on strain, species, preparation process, and cell wall fraction. Demonstration of potent anti-inflammatory effect of the beta-glucan fractions or of pure beta-glucans from C. albicans (PLoS One);

5) the demonstration, in a cohort of 41 Crohn's disease families (129 patients and 113 healthy relatives), that patients and their first-degree healthy relatives are more frequently and more heavily colonized by C. albicans compared to controls (Am. J. Gastroenterol.);

6) the demonstration that variants of genes NOD1 and NOD2 have divergent associations with familial risk of Crohn's disease and regulation of the humoral response towards the yeast Saccharomyces cerevisiae (Inflamm Bowel Dis);

7) the development of new molecular tool for the identification of rare yeasts (J Mol Diagn) and of new biomarkers for the diagnosis of invasive candidiasis (European patent).

Assessment of the team's academic reputation and appeal

The team has a very good academic and international reputation in the field of mycology and mannan/glucan biology and host modulation attested by:

- conference invitation and citations in international articles: 84 presentations and posters.
- very substantial numbers of public (ANR, FP7-ERANET, FP7 Health; AVIESAN-SANOFI, PHRC) and private grants.
- organisation of national meetings (SFM, RICAI, SFI).

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

A very good integration in the economic environment is indicated by several research and clinical programs in partnership with industry and the hospital. One important strength of the team is the development of patented methods for diagnosing Candida infections (patents filed by a private company), for diagnosing fungal diseases, and for modulating inflammatory diseases.

Assessment of the team's organisation and life

The team has a good organisation with coherent scientific objectives for the size of the team. It will be led by a new leader involved in both clinical and basic research. The team has a weekly lab meeting and participates actively in the scientific animation of U 995 by editing a periodical letter of general information, by managing U 995 website, and by coordinating “hygiene and safety” rules for U 995.

Assessment of the team's involvement in training through research

Team members contribute effectively to training through research. Two PhD theses were defended since 2008 and two are on-going which are all associated with several publications and in one case with a patent. The team has a strong implication in teaching fundamental and medical parasitology/mycology (Université Paris 6). Team-members:

1) teach a “Biology-Health, Genetics and Microbiology” course at the Lille 1 and Lille 2 Universities;

2) are in charge of the theme “Microbial envelopes” of the Master year-2 training in “Drug Design” (Lille 2 and Louvain Universities);

3) are member of the scientific committee of the Lille Doctoral School “Biology, Health”. They regularly participate in theses’ committees for the Doctoral School “Biology, Health".

Assessment of the strategy and the five-year plan

The team presents three main objectives.

The first concerns the relationship between structure and activity of glycans of yeast’s wall using genetically engineered mouse models to assess the regulation of the host response through lectin receptors expressed on immune cells. One original aspect is the impact of Gal-3 glycosylation on the polarization of macrophages.

The second objective is to assess the role of fungi in triggering or maintaining inflammation in Crohn’s disease and notably to assess association with polymorphisms of innate immunity genes linked to Candida colonization.

The third objective is to identify new biomarkers of invasive candidiasis.

Overall this is a coherent strategy taking advantage of the skills of the group in C. albicans biology and of the interactions with other teams in the center, notably team 1, to provide insight into the inflammatory response induced by C. albicans and to promote the emergence of clinical and therapeutic applications.

Conclusion

- **Strengths and opportunities:**

- excellent expertise in the field of cell wall glycoconjugates in yeasts and the role of mannans and glucans in modulating the host;

- complementary medical and scientific expertise;

- access to a large spectrum of clinical isolates;

- strong interactions with team 1, expert in inflammatory bowel diseases analysis and care.

- **Weaknesses and threats:**

Few senior researchers.

- **Recommendations:**

The recruitment of a full time scientist would help to strengthen the team and to implement mechanistic approaches.

Team 3: Immunity, inflammation and fibrosis in auto- and allo-reactivity

Name of team leader: Mr Patrick VERMERSCH

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	13	16
N2: Permanent EPST or EPIC researchers and similar positions		
N3: Other permanent staff (without research duties)	8	10
N4: Other professors (PREM, ECC, etc.)	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)	3	1
TOTAL N1 to N6	**25**	**28**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	10	10

• Detailed assessments

Assessment of scientific quality and outputs

The work of team 3 focuses on:

1) human immune-mediated diseases related to self-reactivity (multiple sclerosis and systemic sclerosis), to allo-reactivity (renal or stem cell transplantations), or both (chronic graft-versus-host diseases);

2) chronic, unexplained hypereosinophilia.

The team's strategy is based on the analysis of large cohorts of patients followed by clinical partners (Departments of Neurology, Clinical Immunology, Internal Medicine, Haematology, and Nephrology) and by a "French eosinophil network" coordinated by the team. Its scientific production highlights the strong orientation and

forces in translational research aiming at defining biomarkers and therapeutic targets or protocols, notably:

• Immunophenotyping and immunoproteomic approaches have allowed to identify original predictive biomarkers:

a. in multiple sclerosis (MS) with I) an abnormal phenotype of circulating B cells, II) a abnormal repertoire of antibody responses to self-antigens, which discriminates between healthy subjects and MS patients, III) an IgG auto-antibody signature predictive of relapse in patients with a first clinical episode of MS;

b. in fully HLA-matched bone marrow allografting, with I) the identification of the risk of GVHD conferred by the transfer of a high proportion of CD4+ CCR7+ naïve T-cells, and II) the predictive value of IL-7 and IL-15 plasma levels for both acute GVHD and relapse;

• Interesting data have been obtained in renal transplantation showing the lesser toxicity of Tacrolimus compared to calcineurin inhibitors.

Overall a very good output attested by the publications of the team, which include 236 original papers (78 with a team member as first and/or last or co-last author) and 44 review articles. Experimental and preclinical work was published in good or very good journals as first or last author (e.g. Neurology, J Am Soc Nephrol, Ann Rheum Dis, Arthr Rheum). Several therapeutic trials or proposals published in outstanding journals (e.g. NEJM and Lancet Neurol) but in a collaborative manner.

Assessment of the team's academic reputation and appeal

The team has an excellent international academic reputation in the field of multiple sclerosis. Its very good visibility is attested by:

1) several invitations at international meetings and at seminars in national and foreign universities (8-10 each year);

2) leadership position of the future team leader in clinical trials in multiple sclerosis;

3) coordination of national (hypereosinophilia and Scleroderma) and international (Scleroderma) networks;

4) organisation of a meeting for the European Federation of Immunogenetics (Lille 2012).

The team's members have important responsibilities at the local, regional and national level (INSERM, ANR). The future team-leader is Vice President of the Université Lille 2. A member is chairman of the "Societé Francaise de Greffe de Moelle et de Therapie Cellulaire".

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

This team is very active in interacting with its social environment. It has developed associative structures (e.g. "Orphéos" for hypereosinophila) and local and national clinical reference centers (for multiple sclerosis and for "Rare Neuromuscular Diseases"; competence center for "Thrombotic Microangiopathy", National Reference Center for "Rare Auto-Immune and Systemic diseases", FEN). It has also organized meetings for the general public in France, in particular in Nord-Pas-de-Calais. It also created a web site and audio-visual documents for patients and for hospital staffs (e.g. preparation for transplantation of allogeneic stem cells). No patents are described but the team has obtained substantial financial support from biotech/industrial and pharmaceutical companies, which attests of a solid interaction with its economic environment.

Assessment of the team's organisation and life

Coherent organisation with a balanced distribution of researchers and technical staff (6 persons) between the different projects and the sharing of technical tools (cytometry and immunoproteomic).

Assessment of the team's involvement in training through research

The team has a very good involvement in training. Thus, six PhD theses were defended since 2010,and four are on-going. Four post-docs were trained between 2010 and 2013. Team members are responsible for programs and

courses in Research Masters (years 1 and 2) and are members of the examining board of "Biology, Health"; Doctoral School Lille. In Master year 1, they participate in courses on Basic Immunology and on Immunopathology.

Assessment of the strategy and the five-year plan

A new, experienced, and well-recognized leader in the field of immune-mediated neurological diseases has been chosen within the team to take the succession of its former leader. In line with the translational research strategy led in the past, two main axes are proposed:

I) to extend the identification of specific autoantibody-signatures that could serve as biomarkers for other auto- and allo-responses diseases (neuromyelitis optica (NMO), sclerodermia, chronic graft versus host disease, chronic allograft renal dysfunction) or to dissect various types of hypereosinophilia, work in line with the expertise of the group. This constitutes a potentially promising approach given the team's results in MS and the presence of autoantibodies in many immune-mediated diseases even when tissue damage is T cell dependent.

II) to define new therapeutic strategies:

1. for neurological autoimmune diseases:

a) as a follow-up of the team's results in MS, it proposes to test if protection against neuronal damage can be obtained by promoting regulatory B-cells. It has already identified a promising target and is comparing the effect of different compounds *in vitro*. Best candidates will be analysed *in vivo* in the EAE mouse model of MS in which they observed changes in serum auto-antibodies and B-cell homeostasis, by combining cerebral imaging with classical methods;

b) in collaboration with team 1, team 3 will investigate (I) if alterations of intestinal homeostasis can modulate neurological diseases as suggested by its preliminary results and in keeping with recent data in the literature; (II) if the parasite-derived protein (identified by team 1) that alleviates inflammation in mouse IBD models, can also improve EAE.

2. in allogeneic cell transplantation.

Most notably, the team wishes to define more precisely how $CD4^+$ $CCR7^+$ T cells can compromise reconstitution.

Overall, this is a very good project and the logical follow-up of previous work relying on strong interactions with clinicians, on their access to large cohorts of well-characterized patients, on a strong interface with the Hospital Immunology laboratory, and on interactions within other teams within the center. Experimental models are largely set up. The experts committee has however noticed that the objectives are very broad and that it might be worth to focus on the most promising topics and to implement mechanistic approaches.

Conclusion

- **Strengths and opportunities:**

- excellent expertise in translational research to define biomarkers and to test potential therapeutic targets in neurological and immunological diseases;

- excellent interactions between members of the team and industry, as well as with other teams of the center.

- **Weaknesses and threats:**

A very broad spectrum of projects proposed by a team lacking full-time scientists and whose members have heavy clinical and academic duties.

- **Recommendations:**

Recruitment of (a) full-time researcher(s) to implement mechanistic approaches focused on the most original project(s). Of note, there is a good perspective to recruit an experienced full-time scientist.

Team 4: Nutritional modulation of inflammation and infection

Name of team leader: Mr Frédéric GOTTRAND

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	2	2
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)	5	5
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		1
N6: Other contractual staff (without research duties)	1	1
TOTAL N1 to N6	**9**	**10**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	7	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	7	
Qualified research supervisors (with an HDR) or similar positions	7	7

• Detailed assessments

Assessment of scientific quality and outputs

Team 4 performs very good translational work on the nutritional status of European adolescents based on a cohort of 3000 subjects (FP6 project). It investigates the interactions between nutrition and epithelial inflammation in cystic fibrosis (CF) and inflammatory bowel disease (IBD). It develops pertinent mouse models of malnutrition and lung inflammation to test nutritional strategies and has obtained convincing data that are only partially published.

The results of the team show the beneficial effect of:

1) polyunsaturated fatty acids n-3 PUFA (EPA and DHA) on lung function and mortality in wild type mice and mice deficient for the *Cftr* gene (responsible for cystic fibrosis) challenged by an acute or chronic respiratory infection with *Pseudomonas aeruginosa*. They suggest an effect via modulation of mucus composition;

2) pAOS prebiotics on mortality, lung function, and inflammation measured at the level of broncho-alveolar fluid and lung bacterial load, as well as on the microbiological, inflammatory, and lung function-responses after reinfection.

Authors indicate 241 original and review publications, 30 of which are ranked A and 49 B according to SIGAPS. Most articles concern the translational work. Eight articles (Plos One, Histochem Cell Biol, J Nutrition, Mol Phylogenet Evol : IF 2.6 to 4.1) since 2009 concern the experimental work.

Assessment of the team's academic reputation and appeal

The team has a well-established international reputation in the field of Paediatric Nutrition, with active involvement in the European FP6 project HELENA, in editorial boards of journals (JPGN), in scientific committees at national or European levels (e.g. ESPGHAN). It co-organized two international congresses on paediatric nutrition.

Large amount of funding from Europe, PHRC, AFA, Broad Medical Research Programme (USA), and Aquimer competitiveness pole also attests of the team's solid reputation.

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

The team's members are long time major actors as co-authors of several European and French nutrition recommendations for children (on e.g. breast feeding, formula, allergies, cystic fibrosis) and communicate to the population for a healthy nutrition in infants, children, and adolescents. They participate to advisory committees for authorities at national (Afssa/Anses, NDA) and European level (EFSA). The team has numerous contracts with food companies. The team indicates that one patent is under examination by the local SATT. Overall these activities attest of a very good integration of the team in the social economic and cultural environment.

Assessment of the team's organisation and life

The team is well organized with weekly meetings for projects and organization as well as journal clubs for students. Seminars are co-organized with U995, and a scientific retreat once a year. The team has strengthened its forces with the recruitment of one technician and one engineer with an HDR.

Assessment of the team's involvement in training through research

Seven PhD-theses were defended since 2008. The team's members have an important teaching activity in the fields of paediatric nutrition and inflammatory bowel disease, including for health professionals (i.e. nurses, dieticians, medical students). They participate to several Master year 2 courses, and to two university diplomas.

Assessment of the strategy and the five-year plan

The team's project is highly relevant to clinical questions. It aims at substantiating the role of polyunsaturated fatty acids and mucus modulation in lung and intestinal inflammation and is based on pertinent models (set up during the previous contract) and on clinical studies. Indications provided suggest a good feasibility. The project is well integrated in the global project of the center.

Three main objectives are put forward:

1) the study of the role of early nutrition to prevent inflammation in the lung and intestine using an existing model of post natal growth restriction;

2) analysis of the effect of nutritional intervention on graft-versus-host disease in patients;

3) analysis of the role of mucins in lung inflammation. Preliminary results of the team indicates good feasibility of the project.

Conclusion

- **Strengths and opportunities:**

- interesting experimental models;

- promising preliminary results.

- **Weaknesses and threats:**

- senior researchers have heavy medical and academic duties;

- in this context, the lack of full time scientists represents a situation that may impair the efficacy of mechanistic studies.

- **Recommendations:**

It will be necessary to further implement mechanistic approaches. In this regard the recruitment of a full-time scientist would be useful.

Team 5: Inflammatory digestive diseases and environmental risk factors: Epidemiology and functional analyses.

Name of team leader: Ms Corinne GOWER-ROUSSEAU

Workforce

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

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

• Detailed assessments

Assessment of scientific quality and outputs

Team 5 is a newly formed team originating from U 995's team 1 and a PH from EA 2694 and centered on the epidemiology of IBD. The basis of the project is the highly renowned EPIMAD registry.

The listed publications since 2008 consist of 34 original papers including reviews and 77 published abstracts (40 posters and 37 oral presentations). Generally, the scientific production of the team highlights the orientation on epidemiology and demonstrates the strong forces and possibilities of the group. The epidemiological studies are published in good and very good journals (7 in journals with IF > 10 such as Gut, Gastroenterology, PLOS Pathogens, Nat Rev Gastroenterol, Hepatol., and 17 with an IF > 5).

The team has contributed significantly to the evolvement of epidemiology in IBD based on the EPIMAD cohort consisting of more than 23000 patients with novel descriptions both in paediatric IBD and in the elderly. Emphasis has been placed on the study of clinical predictors of disabling disease in paediatric IBD and on the ethiopathogenesis of IBD. Furthermore, experimental studies have been performed on the effect of aluminium on inflammatory responses and mucosal healing, on identification of antibiotics, and on other environmental factors affecting inflammation. The major contribution of the group is establishment of a large population based inception cohort of IBD patients and the finding of a severe prognosis of paediatric Crohn´s disease. The prognosis is characterized by a severe, extensive phenotype with a greater risk for disease extension by location and surgery than previously anticipated.

The team also performed an epidemiological study of the role of aluminium in Crohn's disease. It strengthened this project with an evaluation of the effects of aluminium in a mouse model of IBD.

The team's work on paediatric IBD has prompted an Editorial in 2008 in the leading gastroenterology journal Gastroenterology.

Assessment of the team's academic reputation and appeal

The team has an excellent academic reputation in the field of IBD epidemiology based on the EPIMAD registry. Two papers in the journal "Gastroenterology" and one in "Gut" and presentations of 77 posters and oral communications best illustrate its activity and visibility.

The team has also received substantial financial support from a number of public agencies and private foundations (e.g. ANRS, PHRC, Inserm).

The team leader has important responsibilities at local, national and international level (principal investigator of national and regional research programmes, member of IPNIC, member of the epidemiological committee (EPICOM) of the European Crohn's and Colitis Organisation (ECCO).

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

The team has a good integration in the regional and economical network; it has acquired substantial grants from pharmaceutical industry.

Assessment of the team's involvement in training through research

During the past five years, the members of this novel team have trained 32 students, resulting in two PhD-graduations, three are on-going. Seven MD theses devoted to IBD were defended and another four are on-going in the same field. Also two pharmaceutical theses were defended. Five university diploma-students and six Master year 1 and three Master year 2 students were trained.

Teaching activities are centered around medicine and pharmacy courses on gastroenterology and public health. Regular meetings for PhD students and Journal Clubs are organized.

Assessment of the strategy and the five-year plan

The objectives of the team's project are to participate in:

1) the identification of patho-physiological factors (environmental, biological, immunological and bacterial/fungal) of inflammatory diseases;

2) the investigation of biomarkers of early inflammatory disease and disease progression;

3) the development of new treatments.

This will combine:

1) a macro-environmental approach for the identification of IBD risk factors aiming at finding environmentally pollutants and risk factors (an epidemiological interventional study of possible pollutants);

2) a micro-environmental approach to isolate predictive biomarkers of a disabling course of and of developing Crohn's disease (examining serology, microbiota and genetics in paediatric and elderly-onset patients).

Besides the epidemiological approach, the project will involve two experimental models, an established mouse model and a model based on zebrafish. The extrapolation of this model on mammals remains to be confirmed.

The project will necessarily involve a lot of external collaborations in order to analyse the enormous amount of data that will be created. Collaborations are indeed planned for data management and biostatistics, for the development of mathematical models for scan statistics and geo-modelling, for the analysis for environmental factors.

Conclusion

- **Strengths and opportunities:**

- highly original project with the possibility of expanding the field of risk factors and disease modifiers in inflammatory bowel disease;

- project is feasible in the new framework of the to be created Research Center, in which closer collaboration with experts will be possible.

- **Weaknesses and threats:**

- the project will be very time- and cost-consuming;

- low number of permanent team members and with heavy teaching duties;

- lack of experts in biostatistics and mathematics;

- possible lack of extrapolation of the zebra-fish model to mammals.

- **Recommendations:**

- allocate more manpower, especially in the field of biostatistics/mathematics and geo-environment in order to ensure success of the project;

- strengthen the staff of full-time scientists;

- strengthen the team's expertise in biostatics and mathematics.

Team 6: Glycation: from inflammation to aging

Name of team leader: Mr Eric BOULANGER

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	4	3
N2: Permanent EPST or EPIC researchers and similar positions		
N3: Other permanent staff (without research duties)	1	2
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1
N6: Other contractual staff (without research duties)		2
TOTAL N1 to N6	**6**	**8**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

Listed production of the two EA teams that will constitute this new team includes 172 original papers and 15 book chapters. Besides a majority of clinical research papers, both teams have also produced experimental studies on animal models (rodents) and on *in vitro* models (HUVEC endothelial cells, cardiac myocytes), amounting to 15 % (EA 2693) and 25 % (EA 4484) of papers during the past five-year period, with mean impact factors of 2.2 (EA 2293) and 3.6 (EA 4484). Clinical productions include publications as co-authors in excellent journals as NEJM, Lancet Neurol, Lancet Infect Dis, Nat Med, BMJ, Ann Inter Med, and Circulation. This production highlights the strong activity of both joining teams in translational research converging with clinical studies to identify therapeutic targets for prevention of aging-associated cardiovascular dysfunction.

The most important contributions by the two joining and merging university teams (EA) have been made along six axes:

1) Role of mitochondrial metabolism and pro-apoptotic signalling in myocardiac dysfunction;

2) Role of mitochondria and macrophage migration inhibitory factor in hypoxia;

3) Induction of endothelial dysfunction by dietary glycation products;

4) Glycation biomarkers of aging and obesity;

5) Implication of glycation products and their specific receptor RAGE on aortic sclerosis;

6) Clinical study of some autoimmune diseases.

Assessment of the team's academic reputation and appeal

The teams' visibility is attested by 55 oral conferences and by congress and symposium organization by the future team's leader:

I) "Aging and anti-aging non-inflammatory proteins" symposium at the 2009 Congress of the International Association of Geriatrics and Gerontology (IAGG);

II) a novel recurrent "Biology of Aging" Symposium at the annual Meeting of the French Society of Geriatrics and Gerontology (SFGG) in Paris (2012, 2013).

Attractiveness of the teams' research has resulted in several local, national, and international collaborations.

Several contracts have been obtained from public agencies or foundations.

Attractiveness is also attested by hosting foreign researchers (for EA 2693: a Brazilian post-doc, two PhD mobilities, one invited professor in 2014).

The future team's leader is Vice-President for international relationships of Université Lille 2.

To be noted also, the future team's leader has attracted to the Université Lille 2 a part of the national Master year 2 training "Biology of Aging", which is headed by Université Paris-Descartes and has a double aim: to train young MDs (at the Internship level) to the experimental approach and to sensitize pre-doctoral students in molecular biology to clinical challenges in Aging Biology. This academic "transfer" was made possible with a double sponsorship: financial support of DigestScience Foundation and academic contribution of several staff-scientists/physicians of the U 995.

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

Very good integration: both joining university teams have developed diversified partnerships, including fund raising activity, with regional pharmaceutical companies and civil communities.

Assessment of the team's organisation and life

In the previous five-year contract, EA 2693 was holding two scientific lab-meetings per month.

Assessment of the team's involvement in training through research

Indicating a very good involvement in training through research, the two joining teams have trained four PhD students and several Master students during the past five-year contract. EA 2693 manages the "Nutrition and aging" course of the National "Biology of Aging" Master year-2. This team also organizes lectures for Biology & Health Master of Lille-2 (M1-M2 levels) and an "Initiation to write articles" in Lille-2 School of Medicine.

Assessment of the strategy and the five-year plan

Both joining EAs had similar scientific strategies, i.e. based on strong interactions with clinics and the general goal to identify new mechanisms underlying cardiovascular dysfunction which should provide new targets for

interventional improvement of aging. The team proposes a clearly described five-year project on the implication of glycation products and mitochondrial dysfunction in inflammation and aging, which will involve three axes:

1) Glycation products, from organs to pathophysiology:

a. assessment of functional and structural changes by ingested AGEs into gut, vessels, heart, kidney, focussing on inflammation and aging. To be noted, aging is now recognized to relate to a global inflammation rise at the organism level;

b. investigation of mechanisms underlying impairment of mitochondrial energetics by exposure to glycation products.

2) Therapeutic screening models. The team's specific background about endothelial cell biology will be used to develop novel biomarkers of proinflammatory cell responses and aging for human clinics. The well-validated HUVEC model of EA 2693 will be completed with import of Caenorhabditis elegans model, for further assays of antioxidants and RAGE antagonist drugs;

3) Auto-immunity and AGE (Advanced Glycation End-products)-related markers. This aim will consist in elucidating the relationship between AGE and autoimmune antiphospholipid syndrome (APS) by using in vitro and murine models.

This project is perfectly feasible. It consists in developing some of the strongest perspectives from recent research activity of both to be fused university teams and it converges with the global scientific objectives of the new Research Center about aetiology and therapy of inflammatory diseases. It is also in direct continuation of previous research specialties of both merging teams. More precisely:

- axis "key pathophysiological factors (…alimentary, biological…)": already available knowledge in nutrition-biology prompts ingestion of AGEs as a priority, although not unique track to follow in order to decipher the unknown aetiology of inflammatory bowel disease.

- axis "biomarkers of early inflammatory diseases": involvements of AGEs and their receptors (from EA 2693) and biochemical pathways of apoptosis and mitochondrial metabolism (from EA 4484) into inflammatory processes in general are already well established. Mere application of tools and scientific expertise from the two merging university teams to inflammatory bowel disease and former U 995's experimental models will therefore provide original and warranted results.

- "development of new treatments" for clinics falls in the general purpose of both merging university teams. Previously developed partnerships with agro-food and pharmaceutical companies show the efficacy of such strategy.

Conclusion

- **Strengths and opportunities:**

Inclusion of the members from previous university teams EA 2693 and EA 4484 into the novel Research Center for the next contract truly strengthens the project because it brings:

I) additional tools and expertise for research of etiological mechanisms and biomarkers of inflammatory disease;

II) additional staff members who have been working since many years in the same professional line as previous U 995 members (translational research combining clinical studies and experimental research on animal and cellular models);

III) a specific supplement of visibility and clinical research networking in fields that are complementary and valuable for the global scientific project of "Center on inflammatory Diseases" of Lille.

- **Weaknesses and threats:**

The integration of EA 4484 staff, tools, and models in the scientific project of team 6 still needs to be completed to fully benefit from a recognized expertise in biochemical pathways of apoptosis and mitochondrial metabolism, and heart cyto-physiology.

- **Recommendations:**

- scientific integration of the two merging teams should be fostered;

- recruitment of full-time scientific researcher(s) would be useful to strengthen the team and to sustain mechanistic approaches.

Team 7: Therapeutic innovation targeting inflammation

Name of team leader: Mr Philippe CHAVATTE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	7	9
N2: Permanent EPST or EPIC researchers and similar positions		
N3: Other permanent staff (without research duties)	5	5
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	4
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**15**	**18**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	13	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken	5	
Qualified research supervisors (with an HDR) or similar positions	9	9

• Detailed assessments

Assessment of scientific quality and outputs

Team 7 will be created for the upcoming research project by combining researchers from EA 4481 (Interdisciplinary Research Group in Therapeutic Innovation and Optimization) and EA 4483 (Impact of the chemical environment on human health). Both teams have been collaborating with U 995 over a couple of years. It is compiling research from different fields (chemists, pharmacists, and medical doctors) focuses on the design of new anti-inflammatory compounds, namely PPARγ-modulators and CB2-agonists as well as drug delivery approaches in order to achieve a more selective delivery of the drug towards the inflamed tissue.

Overall the scientific production of the two teams is of very good level as attested by 90 publications including 84 original articles in specialty journals of IF between 0,5 and 7.6 (including 4 articles in Journal of Medicinal Chemistry, the best journal of the specialty, and as co-authors in PNAS (IF 9.7), Journal of Allergy and Clinical

Immunology (IF10)), 6 reviews, 4 book chapters and 9 conference proceedings, 36 invited conferences, and 91 written or oral communications over the period 2008-2013.

The teams claim the following achievements:

a. development of new modulators of PPARs as they appear as potential therapeutic targets for the treatment of many diseases such as diabetes, obesity, and dyslipidemia. One compound, exhibiting an anti-inflammatory activity 100 to 150 times greater than 5-ASA in an experimental colitis model, is tested by a private company as a drug candidate, currently in phase 2;

b. development of CB2 agonists and FAAH inhibitors for their use in IBD. Several compounds have been patented and the group is currently trying to exploit the potential of these new chemical entities. It can be mentioned that this project was substantially funded by several grants such as ANR Emergence CAB-MICI or an OSEO;

c. development of new FTase and tubulin inhibitors in a strategy of association for cancer treatment;

d. development of nanoparticles for different drug delivery purposes.

Assessment of the team's academic reputation and appeal

The teams have a very good academic level for both chemistry and drug delivery, as attested by 36 invited conferences, 9 conferences proceedings and 4 book chapters, the organization of a summer school and of several conferences (French Romanian Colloquium on Medicinal Chemistry, Journées Francobelges de Pharmacochimie, Conférences Européennes du groupement des pharmacochimistes). One member has received the L'Oreal Unesco women in science prize 2009.

The team members have attracted a substantial number of public grants (e.g. FP7, two "ANR Emergence", two "ANR Blanc", two OSEO) and also private funding over the past five years.

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

The joining teams have excellent interactions with the social, economic and cultural environment: they have submitted 6 patent applications and devote a large of their activity to projects with expected economical benefit, The exploitation of the new chemical compounds interacting with PPAR has a high economical potential and could be very promising when passing the clinical phase 2. The team has participated in the promotion of research and innovation through several operations of communications for the "grand public" (Fête de la science Rencontres étudiants entreprises , Salon Santé Nord, etc.). One member has been expert for the European Parliament in the context of the legalization of Marijuana.

Assessment of the team's organisation and life

Team 7 is a new gathering of researchers from two university teams and needs to establish a novel infrastructural background. It proposes several measures in terms of personnel changes and has already dealt with certain changes (e.g. retirement). The number of permanent staff is sufficient to execute the proposed research projects.

Assessment of the team's involvement in training through research

The two teams have strongly contributed to training by research with 13 PhD theses defended since 2008, all with several articles of IF between 2.3 and 5.6. Four PhD theses are on going. 26 Master year 2 students have been trained.

Team members teach at the "École des Hautes Études d'Ingénieur" and manage four degrees at Université Lille 2 including a- DU "Techniques d'Elaboration et d'Analyse des Biomolécules", a Master 1 and a Master 2 (Professional & Research) in Drug Design, and a new course called Master in Drug Design for MD and pharmacists.

Conclusion

- **Strengths and opportunities:**

Team 7 has already strong interactions with team 1 and has shown its expertise in developing compounds in the field of IBD. It has produced new chemical entities with high potential to reach the market.

- **Weaknesses and threats:**

- dispersion reduces manpower available for each proposed project;

- the drug delivery group is small and does not yet have expertise in the field of IBD.

- **Recommendations:**

- the drug delivery subgroup needs to be strengthened;

- given heavy teaching and administrative activities, efforts should focus on high priority projects.

5 • Conduct of the visit

Visit dates:

Start: Thursday December 19th 2013 at 08.30 am

End: Friday December 20th 2013 at 01.00 pm

Visit site:

Institution: Faculty of Medicine

Address: Pôle recherche, Université Lille 2, Campus Hospitalo-Universitaire, Lille

Conduct or programme of visit:

Thursday, December 19th 2013

08.30 am	Closed-door meeting: expert committee members and AERES Scientific Delegate (DS)
09.00 am	Presentation by Mr Pierre DESREUMAUX, director: past activity and projects
09.30 am	Team 1 'IBD physiopathology and development of new therapeutic targets' (head: Mr Laurent DUBUQUOY)
10.15 am	Coffee break
10.45 am	Team 2 'Fungal-associated invasive and inflammatory diseases' (head: Mr Boualem SENDID)
11.15 am	Team 3 'Immunity, inflammation, and fibrosis in auto- and allo-reactivity' (head: Mr Patrick VERMERSCH)
12.00 pm	Team 4 'Nutritional modulation of inflammation and infection' (head: Mr Frédéric GOTTRAND)
12.45 pm	Lunch-buffet and visit of posters
02.00 pm	Team 5 'IBD and environmental factors: epidemiology and functional analyses' (head: Ms Corinne GOWER-ROUSSEAU)
02.45 pm	Team 6 'Glycation: from inflammation to aging' (head: Mr Eric BOULANGER)
03.15 pm	Team 7 'Therapeutic innovation targeting inflammation' (head: Mr Philippe CHAVATTE)
04.00 pm	Concluding remarks by the director, Mr Pierre DESREUMAUX
04.15 pm	Tea-break
04.30-06.00 pm	Closed-door meeting of the experts committee and DS

Friday, December 20th 2013

08.30 am	Meeting of the experts committee with representatives of Université Lille 2, Inserm, CHRU, Région Nord – Pas de Calais, HEI.
09.00 am	Meeting of the experts committee with representative of the Lille Doctoral School Biology and Health
09.15 am	Three parallel meetings of the experts committee with: • PhD students and postdoctoral fellows • Engineers, technicians and administrative assistants (in the presence of Mr Michel RAUCH, Inserm CSS7 and Ms Valérie DESSIRIER, Inserm CSS5) • Researchers with permanent position (except the director and team-heads)
10.00 am	Coffee-break
10.30 am	Closed-door meeting of the experts committee and DS with the unit's director, Mr Pierre DESREUMAUX
11.00-13.00 pm	Closed-door meeting of the experts committee and DS

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 11 avril 2014

V/Réf. : E2015-EV-0593560Z-S2PUR150008773-006823-RT

Objet : Observations de portée générale sur le rapport d'évaluation de l'unité *Inflammation : regulation, interaction with nutrition, and therapeutic innovation*

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 *Inflammation : regulation, interaction with nutrition, and therapeutic innovation* pour la qualité de l'évaluation effectuée les 19 et 20 décembre 2013 par votre comité d'experts.

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

Vous trouverez ci-dessous les observations de portée générale sur le rapport d'évaluation de l'AERES, émises par le Directeur de l'unité *Inflammation : regulation, interaction with nutrition, and therapeutic innovation.*

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

Pr. Xavier VANDENDRIESSCHE

Université Lille 2
Droit et Santé

Centre Hospitalier Régional
Universitaire de Lille

Instituts thématiques
Inserm
Institut national
de la santé et de la recherche médicale

U 995 Inserm
Pr. Pierre DESREUMAUX, directeur

Lille le 31 mars 2014

Réf : S2PUR150008773 - Mécanismes de régulation et interactions avec la nutrition et l'innovation thérapeutique - 0593560Z

Observations about the Aeres report

We thank the evaluation committee for their pertinent expertise and constructive observations. We appreciate your positive overall assessment of the unit and of the 5-year plan strategy of the future Center on Inflammation LIRIC. Our scientific objectives remain centered on inflammation including only complementary bench to bedside approaches without scientific dispersion.

We agree that one important objective for the next 5 years will be the recruitment of full-time researchers. With your input and the support of INSERM, Lille University, Lille University Hospital and the Region Nord Pas de Calais, we expect to find opportunities for the funding of talented scientists. We are already very happy to announce the arrival of Dr Mars Lennart CR1 INSERM in the LIRIC in the next months and also the wish of Dr Frederic Tessier (from the Institut Polytechnique LaSalle Beauvais) for joining our Center. Our goal is to recruit at least 1 new full time researcher per year in the next 5 years.

Concerning the scientific axis "Glycation: from inflammation to aging", Dr Remi Nevière will join the group 6 to give his skills in the fields of apoptosis and mitochondrial metabolism. We hope also that Dr Tessier will soon be recruited to strengthen the team by giving his expertise in glycation product synthesis.

Concerning the team 7 entitled "Therapeutic innovation targeting inflammation", their scientific objectives are focused on four medicinal chemistry projects involving CB2, P2X7, NKT and NOD1. Organization of each project is well defined and will be reinforced by the recruitment of an assistant professeur in september 2014. The drug delivery group directed by Pr Didier Betbeder has an important and complementary activity with the team 7 and with the whole LIRIC Center. Its recent integration in the LIRIC is remarkable and fruitful since 2 new grants have been recently funded for the use of nanoparticles in the field of IBD treatment.

Best regards

Le Président de l'Université

Xavier VANDENDRIESSCHE

Pierre Desreumaux

République française

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