LNC - Lipides, nutrition, cancer

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Lipids, nutrition and cancer

From the

Université de Bourgogne

INSERM

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

February 2011

Research Unit

Name of the research unit: Lipids, Nutrition, Cancer

Requested label: UMR_S

N° in the case of renewal: UMR_S 866

Name of the director: Mr. Laurent LAGROST

Members of the review committee

Committee chairman:

Mr. Bart STAELS, Université Lille Nord de France, Lille

Other committee members :

Mr. Patrice CANI, Catholic University of Louvain – Brussels (Belgium)
Mr. John CHAPMAN, INSERM, Paris (France)
Ms. Jacqueline CLAVEL, INSERM, Villejuif (France)
Mr. Juergen ECKEL, University of Düsseldorf (Germany)
Ms. Fiona M. GRIBBLE, University of Cambridge (United Kingdom)
Ms. Fawzia LOUACHE, INSERM Villejuif (France)
Mr. Laurent MARTINEZ, INSERM Toulouse (France)
Ms. Christine PERRET, INSERM Paris (France)
Mr. Rodrigue ROSSIGNOL, INSERM Bordeaux (France)
Mr. Pierre SONVEAUX, Catholic University of Louvain – Brussels (Belgium)
Ms. Ewa NINIO, Paris (France), CSS INSERM representative
Mr. Olivier OUDAR, University Paris 13, Bobigny (France), CNU representative

Observers

AERES scientific advisor:

Mr. Jean GIRARD

University, School and Research Organization representatives:

Mr. Raymond BAZIN, INSERM
Ms. Sophie BEJEAN, Université de Bourgogne
Mr. Bruno CANQUE, EPHE

Report

1 • Introduction

• Date and execution of the visit

The site visit took place in Dijon at the School of Medicine of the University of Burgundy on February 2nd and 3th, 2011. It was conducted by an international evaluation panel of fourteen experts in the scientific fields represented by the eleven evaluated teams.

The visit started by a short presentation of the future INSERM research Center by the director. The center will be organized in eleven teams. Then, each team leader presented the activities and projects of their group during one and a half day of the visit. Before lunch of the second day, the committee, divided in three groups, had separate closed-door meetings with the different personnel categories of the center (three parallel meetings with students/post-docs, technicians/engineers and permanent scientists). The committee also met the representatives of the University of Burgundy (President, Dean of the School of medicine, Director of the EPHE) and with the representative of INSERM. The visit ended with a closed-door meeting of the committee members.

• History and geographical localization of the research unit, and brief presentation of its field and scientific activities

The UMR866 was created as an emerging Inserm research Center in january 2007 emanating from five entities (INSERM U498, INSERM U517, INSERM EMI-106, teams of the Life Sciences Faculty and ENSBANA). The official creation date was january 2008. In 2009, the unit was joined by CIC-EC, CIC-P and an AVENIR team. In january 2010 after the departure of the director, the UMR866 direction was assumed by the present director (also leader of team 11). The proposed center will also have tight connections with EPHE, the University Hospital of Dijon, the George-François Leclerc Center and AgroSup (national school of engineers).

The unit is composed of about 240 people including 110 permanent researchers/teachers in eleven teams, most of them being located in one building of the School of Medicine. This center has several facilities including facilities that are part of the Federative Research Insitute "Santé-STIC" (such as echography of small animals, isotopic mass spectrometry, electron spin resonance, lipidomics,…).
The research center is dedicated to multidisciplinary research and to promote fundamental and clinical sciences in the fields of Cancer, Nutrition, Lipid Biology and Cardiometabolic research with a strong emphasis on inter-disciplinary approaches.

• Management team

The research center will be managed by the current director of the UMR866, assisted by two deputy directors:

Laurent LAGROST, Director

Claire BONITHON-KOPP, Deputy-Director

Carmen GARRIDO, Deputy-Director

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	58	74
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	11	11
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	30	14 (permanents only)
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	20	19.5
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	21.9	
N6: Number of Ph.D. students (Form 2.8 of the application file)	58	
N7: Number of staff members with a HDR or a similar grade	52	66

2 • Overall appreciation on the research unit

- Summary

The Inserm Research Center of Dijon will be composed of about 240 people in eleven teams. There is a mixture of teams from INSERM and teams from the University of Burgundy with tight connections with EPHE, the University Hospital (CHU) of Dijon, the George-François-Leclerc Center and AgroSup (a school of engineers). The main topic of the center is to promote research on fundamental and clinical sciences in the fields of Cancer, Nutrition, Lipid Biology and Cardiometabolic research with a strong emphasis on inter-disciplinary approaches. The unit will be managed by the leader of team 11, assisted by two deputy directors among whom one is also leader of team 3. The unit will be located on several sites. The new center is clearly moving towards excellence. The center recruited young and promising teams with new leaders for many teams. The center will be part of the Federative Research Institute (IFR) through which teams have access to additional technical facilities via its technical platforms, but also additional scientific interactions.

The center should also take an important part in a recent demand of Labex within the PRES Burgundy-Franche comté, if granted.

Finally, the center is well integrated with all the scientific actors of Dijon in the domain of Nutrition and Cancer, in particular with the hospital of Dijon for translational research, but also with the pharmaceutical and food-processing industry.

- Strengths and opportunities

- the center is well organized and is well directed by the current director and his management team;

- attractiveness for promising young leaders coming from abroad, as attested by the INSERM-AVENIR team;

- attractiveness for young researchers at CR or MCF level;

- some strong interfaces between biologists, physiologists and clinicians

- links to the hospital of Dijon provide the opportunity for medically relevant and translational research;

- strong implication in teaching activities on the Health and Sciences campuses of the University of Dijon;

- overall production of the unit is good and impact factors have improved (n=834; XFI = 4.23; citations = 8196; 50% of papers FI >6), however the level of publications of some teams are average and should be improved;

- the center has constituted an independent SAB for scientific guidance;

- collaborations between teams is already effective as attested by joint publications increasing in number and qualities;

- the policy of the center regarding the training of the Master and phD students is satisfactory (one global meeting every two week) and formation is also satisfactory (including Ecole doctorale formation);

- training and participation of young students in international meetings is satisfactory.

- Weaknesses and threats

- international attractiveness for non-French scientists and post-docs is limited for some teams;

- some students consider that the lack of technical personnel forces them to perform activities which delay the advancement of their projects;

- the size of some of the teams is suboptimal; an effort should be made to reach the critical size allowing achievement of the proposal goal;

- the balance between full time researchers and teachers is unbalanced (more teachers than researchers);

- the valorisation could be improved (number of patents is 5).

- Recommendations

- local possibilities for fellowships probably exist at the University of Dijon and the Region, which should be further explored and more actively exploited;

- the participation of some leaders as invited speakers is limited and there is clearly space for improvement with respect of their international visibility;

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	73
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	11
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	0.99
A4: Number of HDR granted during the past 4 years (Form 2.10 of the application file)	10
A5: Number of PhD granted during the past 4 years (Form 2.9 of the application file)	51

- increase the number of post-docs by an active funding policy. The number of permanent researchers is high compared to the accommodation facilities (the ratio of permanent vs. non-permanent researchers is unbalanced and too high);

- funding visibility of some teams is low. Some teams should raise more external funding on the (inter)national level;

- increase the valorisation strategy of some teams.

Production results

(cf. http://www.aeres-evaluation.fr/IMG/pdf/Criteres_Identification_Ensgts-Chercheurs.pdf)

3 • Specific comments

- Appreciation on the results

Quantitatively the research unit produced during the last four year about 680 publications, a number that is constantly increasing when compared to the past. Qualitative analyses show that the overall quality of papers has increased in this last four year period with more than 50% in the Top50% and 15% in the Top10%. The committee deeply encourages the productive teams to continue in this way. A number of teams are encouraged to be more ambitious in their publication strategy, but this appears recently to have been implemented (very recent good papers with high impact). On the research valorization side, the Center has produced 5 patents. The center also largely contributes to research training, with currently 58 PhD students in the laboratories, 51 having obtained their degree in the last 4 year period. Overall the activity of the center has provided a solid contribution in terms of scientific publications, valorization, teaching and training.

- Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners

The LNC Center has reached a good national visibility. This is attested by its efficiency in raising funds from local and national foundations, in particular important funds from La «Fondation de France», la Ligue contre le cancer and la Fondation Française de Cardiologie. It also efficiently attracted funds from the national research agencies ANR and Inca. It is important to note that most of the teams contributed to this overall success (attested by common publications). This is also attested by the attractivity of the LNC center for young researchers or senior teams. From an European and international point of view, a number of teams have ongoing world wide collaborations, and the overall level of European and international grants is good. However, it is noted that a limited number of teams participating in the next four year period are attracting the totality of these international funds. Thus, the international visibility of a number of teams remains insufficient. The relative limited international visibility of the center may also explain the modest number of foreign post-doctoral fellows compared to the number of available scientists with a HDR degree.

- Appreciation on the management and life of the research unit

The general organization of the center appears excellent and discussions with laboratory representatives highlighted the quality of the governance. The scientific animation is very good, with regular internal/external speaker seminars and journal clubs (weekly within each group, monthly with invited speakers, annually with presentation by each team of its main results and projects). Moreover every two years the Center is evaluated by an international scientific advisory board. The action of the present director has been extremely efficient in connecting the center to the local research environment: The LNC center is part of an IFR and it is well implanted in the local and regional research organisations.

The connection with the University of Burgundy, the CHU de Dijon and the center for anti-cancer therapy (CGFL) is also excellent, with a high number of Professors or Assistant Professors being heavily involved in teaching, designing curricula for students and leading the PhD school (Ecole Doctorale). This strong implication at the University of Burgundy is the cause of the good attractiveness for PhD students. However, the drawback is the heavy teaching load on many permanent researchers in the research unit that leads for certain teams to difficulties in term of available research time. Finding solutions to solve this issue, especially for those researcher/teachers that are group leaders, appears highly desirable.

- Appreciation on the scientific strategy and the project

Most of the projects presented are ambitious and promising and must be attempted and ensured for the next four years. Nevertheless, a few teams should try to focus and define priorities between their projects.

The human resources of the center are unequally distributed, but are in line with the announced projects by the teams. In some cases, especially in highly competitive research fields, a number of teams should focus also on mechanistic approaches.

For the long-term perspectives, the LNC center and its director together with his two deputy directors have launched a project aimed to the creation of a new research center, with a hosting capacity of about 11 teams on one site. This research center will be located on the Burgundy University campus, in direct proximity to the Hospital, a location that suits the goal to promote the interface between basic and clinical research.

4 • Appreciation team by team and/or project by project (to be pasted as many as needed)

- Title of the team and name of the team or project leader:

  Chemotherapy, lipid metabolism and anti-tumoral immune response – François GHIRINGHELLI

Past: Team AVENIR – Future: **Team 1**

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	-
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	2	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0.4	0.2
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.8 of the application file)	4	
N7: Number of staff members with a HDR or a similar grade	5	6

- Appreciation on the results

The scientific activity of the team is focused on cancer immunology and immunotherapy. This is a follow-up of a highly productive post-doctoral training of this team's leader in the laboratory of L. Zitvogel (IGR Villejuif), where the leader was a main contributor to the work characterizing the immunogenic cell death induced by some chemotherapeutic agents (Nat Med 2007, Nat Med 2009).

The leader recently joined the IRC 866 at Dijon with an Avenir award (2009). In spite of the only recent creation of the team, he has already been able to bring important contributions, the identification of a new mechanism whereby T Reg control the anti-tumor immune response (JCI 2008), the impact of the level of infiltrating Treg cells evaluated in breast cancer patients (Clin Cancer Res 2008), the demonstration that 5FU selectively kills MSDC (myeloid-derived suppressor cells) and thus restores anti-tumor immunity (Cancer Res 2010) and identification of the way by which MDSC cells mediate their immunosuppressive function (JCI 2010).

Finally, through collaboration with another team of the CRI, they demonstrated that visceral fat is a bad prognosis marker of the response to anti-angiogenic therapy of metastatic cancer patients (Gut 2010).

Altogether, the scientific output of the team is excellent.

The team has recently greatly expanded, being joined by several investigators coming from the CRI 866. At the time of AVENIR creation (January 2009), it was constituted by the team leader and 3 students, it is now composed of 16 persons including 5 researchers all with teaching duties (PU-PH and MCU), 1 engineer, 1 technician, 9 students and one post-doc fellow granted with an ANR "Retour Post-Doc" who will postulate for an Inserm permanent position.

The partnership with L Zitvogel and G Kromer's teams is maintained and this is a positive point for the success of the team.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Although the team leader is young (34 years old), several awards need to be highlighted: obtention of the AVENIR label in 2009, and an ANR "retour post-doc" grant to the post-doc fellow, which emphasize the attractivity of the team to recruit high level scientists.

The capacity to raise funds is also excellent (grants from ARC, LNCC Fondation de l'Avenir, PHRC, ANR)

- Appreciation on the scientific strategy and the project

The project is a continuation of their recent results and will particularly investigate the effects of chemotherapy on two cell populations suppressing the antitumor immune response, the T Reg and the MDSC cells. All the projects have a strong clinical perspective.

The basic research projects will investigate 1) the cross-talk between the MDSC cells and the T-reg in suppressing the antitumor response of the immune system in experimental tumor-bearing animals, 2) the mechanism of action of LXR agonists in inducing an immune anti-tumor response. A third translational project will extend their previous data of the prognostic value of T Reg infiltration in breast cancer by studying a larger cohort of patients.

Not really linked to the immunology field, a clinical research project led in an autonomous manner by one PU-PH who recently joined the team will investigate how to improve the delivery of anticancer drugs through the development of loco-regional chemotherapy. The integration of this research project for the scientific coherence of the whole team project is not obvious.

- Conclusion :

  - Summary

Clearly one of the best and most promising groups of the CRI. Important achievements have been made concerning the role of the antitumor immune response induced by cancer therapy.

  - Strengths and opportunities

Most of the projects provide an important connection between clinical and basic research.

  - Weaknesses and threats

The challenge for this young talentuous team is now to manage a team of increased size with many senior researchers having teaching duties and many students in order to maintain the quality of the research.

  - Recommendations

It will be important:

1) to stabilize the team by the recrutment of (a) permanent research scientist(s);

2) that the team keeps focus on its strengths which deals with the role of the immune response during chemotherapy;

3) to develop more molecular mechanistic approaches applied to basic science.

4 • Appreciation team by team and/or project by project (to be pasted as many as needed)

- Title of the team and name of the team or project leader
  Gene regulation in hematopoiesis and leukemogenesis – Laurent DELVA

Past: Team 4 – Future : **Team 2**

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	4	-
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2.4	1.2
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.8 of the application file)	7	
N7: Number of staff members with a HDR or a similar grade	5	3

- Appreciation on the results

-1- Team 2 corresponds to the continuation of team 4 following the departure of the former director of the CRI. Since January 1st, 2010, Laurent Delva leads this emerging team. The team includes 10 members from which 1PU-PH, 2 CR, 1 technician and 5 PhD students.

The leader is a full time accomplished researcher specialised in the field of the transcriptional regulation of normal and leukemic hematopoiesis. He, together with one CR1 and one PU-PH, has contributed to discover several new aspects of the regulation of hematopoiesis: the role of the ubiquitin ligase Rik1 in heterochromatin formation (Genes Dev 2005), epigenetic control of HOX genes by the functional interaction between MOZ and MLL transcription factors (Oncogene 2007, 2010), the development of the first zebrafish model of acute myeloid leukemia (Exp Haematol 2008, Brit J Haematol 2008), the role of the cellular inhibitor of apoptosis protein 1 (cIAP) in cell proliferation and during macrophage differentiation (Blood 2009, Cell Cycle 2008). In addition several papers have been published in collaboration;

-2- As a result, the record of publications is good, especially considering the small size of the group. In addition, 1 patent has been registered in 2010;

-3-Several scientific communications mostly in France, but also in Europe were given by the leader indicating a good visibility;

-4- thesis were obtained under the supervision of the members of the team;

-5- The team seems to be stable as the three PI have published in common several papers.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team leader is nationally recognized in the field and his work is reasonably cited. His "national visibility" as measured by other criteria such as presentations at national meetings, membership of scientific societies, recruitment of students/postdocs, etc. has been good.

- Appreciation on the scientific strategy and the project

Two main ambitious projects are proposed. The first project which is logical and very exciting is build upon recent (largely unpublished) results on the effect of TIF1-gamma invalidation in hematopoiesis. These recent studies, showing a chronic myelomonocytic leukemia (CMML) like phenotype and the extinction of TIF-1 in CMML patient cells, open interesting perspectives on a possible novel function of TIF1 as a tumor suppressor. The future work will define the epigenetic modifications that are associated with TIF-1 gamma extinction. Using biochemical and molecular approaches, the team proposes to identify the molecular partners and the targets of TIF-1. Another part will address the status of TIF1 gamma in leukemic patients and its role in leukemogenesis. Pursuit of these studies appears promising and should be strongly encouraged.

Another project is dedicated to a second protein, cIAP1. The team has described its implication in gene transcription. The program includes the identification of the partners, its effects on epigenetic modifications, its influence on its partners. Finally, the role of this oncogenic protein will be investigated using mouse models and shRNA strategies.

- Conclusion :

  - Summary

The project is very exciting, ambitious and relevant to human pathology.

  - Strengths and opportunities

The project is original and results from their own research. The team has good knowledge of the field and the translational effort is relevant and of good quality. The recent recruitment of a postdoc fellow will reinforce the team and reflects the attractitivity and the dynamism of this new team. Collaboration with hematological clinicians is a positive point.

  - Weaknesses and threats

Small size of the team.

  - Recommendations

The team should be stimulated to keep focus and define priorities on the different projects and to raise sufficient funds to concretize their projects.

4 • Appreciation team by team and/or project by project (to be pasted as many as needed)

- Title of the team and name of the team or project leader

  Heat Shock Proteins : cell death, cell differentiation and tumorigenic properties – Carmen GARRIDO

Past: Team 2 – Future : **Team 3**

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	3
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	5	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1.4	1.2
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.8 of the application file)	4	
N7: Number of staff members with a HDR or a similar grade	4	6

- Appreciation on the results

This team investigates the role of HSP70 and HSP27 in cancer biology, apoptosis and resistance to therapy. Team 3 produces innovative knowledge on the HSPs and recently proposed new diagnosis and therapeutic strategies based on the inhibition of Heat Shock Proteins in cancer (HSP90 and HSP70 and HSP27). Between 2007 and 2011 the team has published 60 papers in high impact good journals including Nature, Allergy (IF 6.38), Immunology (5.65), J Clin Invest, Cell Death and Differentiation (8.24), Oncogene (7.14), Blood (10.6), Cancer Research (7.6), JBC, Cancer Letter.

In addition, 9 books and book chapters have been produced and the work of team 3 has been presented in several (31) international meetings. The joining members of team 3 have already published 2 papers (Cell Death Diff and Cur Mol Med) with the other members of the team in good journals, demonstrating the capacity of the group to work together.

The team was already present at the creation of the research center and was recently reinforced with 2 permanent and 7 non-permanent researchers.

Team 3 has developed excellent interactions with local partners beyond their own field of expertise (biochemistry). They interact with chemists to develop HSP inhibitors and screening systems.

There is a good collaboration between team 3 and several international teams: team 3 published 30 papers in collaboration in high impact journals since 2007: JCI, Oncogene, CDD, Blood. Team 3 has established collaborations with the Intitute of Photonics in Barcelona and the Ecole Polytechnique Federale de Lausanne, IGBMC Strasbourg, Sheffield University, Vancouver, New York (drug design/testing) and Munich.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

In the last 3 years, team 3 recruited 1 researcher (INSERM CR1), 1 professor (PU), 3 postdocs and 4 PhDs, showing the attractivity of this group. 3 postdocs are from foreign countries and 1 is applying at INSERM for a CR position. Team 3 is funded by 3 European grants, 2 grants from Inca (2), the label "Ligue contre le Cancer team", 2 ANR and other cancer associations. Contracts were also obtained with industry to develop anticancer strategies focused on HSP 70. A contract of Interface with INSERM was also obtained recently.

Team 3 participates in 2 european programs and coordinates research on HSPs.

Team 3 research activity has established new knowledge on the role of small HSP proteins in cancer survival (blockade of apoptosis) and recently in erythrocyte differentiation. From this work, team generated drugs for cancer killing: HSP90 inhibitor 17-AAG and PU-Z8 in phase III and HSP70, HSP27 inhibitors (OGX427) in phase II. These might become new effective drugs for cancer therapy.

- Appreciation on the scientific strategy and the project

The feasability of the proposed project is ensured by the developped expertise in HS¤ proteins. The novelty of studying the role of HSPs in erythrocyte development is made possible by the collaboration with local teams expert in this domain as well as french experts (team of O Hermine – Necker and team of M Fontenay – Cochin). Macrophage differentiation will be investigated in collaboration with the team of E. Solary. The size of the team is in accordance with the two goals.

The projects are funded by ANR and Inca grants, some of which ensure funding for the coming 3 years. C. Garrido has applied to other grants at ANR to support ongoing research. Contracts obtained with the industry support the drug development activities.

- Conclusion :

  - Summary

Team 3 is a very good french team with international visibility. C Garrido, the team leader, is recognized world-wide for her work on small HSPs and she recently developed inhibitors of these proteins to treat cancer. Two drugs are in phase III trial. A large number of postdocs and PhD students have been trained in team 3. The proposed project is highly innovative and opens a new domain for HSP proteins (role in differentiation) with expected impact on human health.

  - Strengths and opportunities

The strength of team 3 is the originality and the specificity of the research project with recognized expertise and leadership in the domain of HSP and cancer, supported by key publications in the highest ranked journals. In addition team 3 has recently produced 3 patents. They concern anti-cancer therapeutic approaches focused on HSP70. The projects are focused on: (1) the role of HSP70 in bone marrow precursor cells: the erythroblasts, the role of extracellular HSPs in diverse pathologies and (3) Diagnosis and Therapy. These projects are innovative, clear, original, focused and with important clinical implications.

  - Weaknesses and threats

The team leader should stimulate research among the less active members of the team.

  - Recommendations

The group of C. Garrido currently develops technological innovations which may lead both to diagnosis and therapeutic tools against cancer. The group should comfort their ongoing innovative research on HSP70 immunology by publishing a leading article in this new field.

4 • Appreciation team by team and/or project by project (to be pasted as many as needed)

- Title of the team and name of the team or project leader
  Nitric oxide and cancer - Ali BETTAIEB

Past: Team 3 JEANNIN – Future: **Team 4 BETTAIEB**

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5	6
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	-	-
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	4	-
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1.4	1.2
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	-	
N6: Number of Ph.D. students (Form 2.8 of the application file)	6	
N7: Number of staff members with a HDR or a similar grade	2	3

- Appreciation on the results

A Bettaieb was recently appointed head of Team 4. The team demonstrates high level expertise in the field of protein S-nitrosylation both in vitro and in vivo. Examples include the identification of b-catenin and Fas as targets of glyceryl trinitrate (GTN)-mediated S-nitrosylation. Two clinical trials were conducted, illustrating the translational dimension of the team and bringing clinical significance. The originality and high quality of the researches are further exemplified by the ability of team 4 to successfully conduct biotin switch assays (only few teams worldwide have this technical expertise) and cutting-edge molecular biology approaches (study of iNOS gene transcription). Team 4 has a good track record with 34 peer-reviewed papers between 2005 an 2010 among which 9 original papers involving team members as first or last author(s), 19 collaborative papers and 7 reviews. Publications were generally of high impact with 2 publications in Gastroenterology (IF = 12.90 and 12.46) followed by 1 Oncogene (IF 6.58), 1 FASEB J (IF 6.40), 1 JBC (IF 5.52) and 1 Mol Cancer Ther (5.17). Productivity could still be improved because several team members have heavy teaching duties. 7 PhD theses were defended between 2006 and 2010, which is fair for a team of this size. There is no mention of scientific communications by team leaders although both PIs organized international meetings. International visibility is thus limited. An expert in zebrafish bioluminescence was recently recruited but is apparently not well integrated (yet) in the team: her researches are not mentioned in past achievements nor in the project.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

No national or international award was reported within the last 5 years. One invitation to a meeting in Paris is mentioned. This is below expectations with respect to European standards. Several grants have been recently secured (CGFL, cancéropôle Grand-Est, ARC 2 yrs, Ligue Grand-Est, Région de Bourgogne FABER). One InCa pre-project was accepted and the project is submitted. Team 4 collaborates with several other teams of U866, is member of a national network (POLYNOM-174), collaborates with other units in France and with 1 European group (FEDER). The number of national collaborations is thus high whereas the number of international collaborations can still be improved. A patent application has been recently submitted (demonstrating other forms of valorization than papers). Phase I clinical trials (under Team 4 leadership) may have a high socio-economic impact.

- Appreciation on the scientific strategy and the project

The project addresses interesting questions (such as the identification of protein targets of S-nitrosylation, their function and their utility as markers of tumor response to GTN and OM-174). It logically builds on the expertise of Team 4. It proposes cutting-edge approaches (such as biotin switch assay) and is translational. Several grants have been already secured. Although these elements suggest that the project is feasible, the choice of murine models (mouse cells and mouse tumors) instead of human tumor cells and xenografts reduces clinical relevance. In vivo experiments addressing the response to OM-174 (but not GTN) justify the use of syngeneic mouse tumors instead of human tumor xenografts (immune response involved). Feasibility of the clinical trial is questionable due to potential species differencies between mouse and human macrophages. Other important caveats to the project are (1) the lack of perspectives for the use of the whole S-nitroso-proteome (only proteins controlling cell survival and death will be analyzed further), (2) the fact that the whole project depends on a collaboration with the Proteomic Platform of the University of Burgundy, and (3) the in vivo use of agonist/antagonists of the identified protein targets (these drugs may simply not exist, may have low tumor bioavailability and uncharacterized pharmacodynamic profiles). The use of transgenic mice is not relevant to test the functionality of S-nitroso-proteins expressed in cancer cells. There is no documented allocation of resources and no proposed time line. The project is original because it uses cutting-edge procedures (such as biotin switch and site-directed mutagenesis) and intends to explore a yet poorly characterized system for posttranslational protein modification that could have important physiological and pathophysiological functions.

- Conclusion :

  - Summary

Past achievements of Team 4 are of high scientific quality, as also illustrated by 2 publications with IF > 12. The new project is original (biotin switch assay is a strong plus giving a unique opportunity to identify S-nitroso-proteomes), is financed, but uses clinically irrelevant models (mouse instead of human) and sometimes inadequate approaches (in vivo use of potentially non-existing drugs and irrelevant use of KO mice). Overall, the scientific rationale for testing OM-174 in the clinics is lacking (iNOS is not expressed in human macrophages). The organization is good (funds available, long-lasting clinical collaborations but few post-docs). The international visibility is limited (organization of international meetings but few invitations, no international award, and very limited international collaborations).

  - Strengths and opportunities

The major strength of Team 4 is its translational and clinical dimensions that demonstrate high-level organizational skills with respect to collaborators including clinicians. The team has high expertise in its field of research. Results were valorized by 1 patent application, thus highlighting the socio-economic benefits of Team 4's works.

  - Weaknesses and threats

Team 4 has a good track record of publications that could still be improved, but little international visibility. The project is original but largely clinically irrelevant (mouse cells and tumors) and some parts (use of transgenic mice, agonists/antagonists that may not exist …) may not be feasible. The clinical trial with OM-174 is not grounded on strong bases (iNOS is barely expressed in human macrophages). The expertise on zebrafish is not properly exploited.

  - Recommendations

The committee strongly recommends that Team 4 focuses on its strength, protein S-nitrosylation. The team should propose a management plan (personnel and timelines). More involvement in international meetings and collaborations is encouraged. Given the significance of the achievements, more publications in more prominent journals is an achievable goal.

4 • Appreciation team by team and/or project by project projet (to be pasted as many as needed)

- Title of the team and name of the team or project leader
  Immunity and obesity-related disorders – Bernard BONNOTTE

Past: Team 1 – Future : **Team 5**

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	12
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	-
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	3	-
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0.4	1.2
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0.6	
N6: Number of Ph.D. students (Form 2.8 of the application file)	10	
N7: Number of staff members with a HDR or a similar grade	3	6

- Appreciation on the results

The team has worked over the last 15 years in the field of immunology, and more specifically on the role of dendritic cells in the context of anti-tumor immunity. Over this period, they have identified different mechanisms by which DC harboring specific phenotypes may play a role on immunosuppressive cells such as Treg. Different strategies for interfering with Treg have been studied, by using either chemotherapeutic tools or activated DC (Killer DC). The originality of the past work resides in the complementary approaches (models) and in the completion of the work: from pre-clinical investigations to clinical studies. The recent discovery that KDC are potentially generated from peripheral blood monocytes, and that these cells are capable to switch their function from killers to messengers or even more to spare non-malignant cells, is of utmost importance for the field. Nevertheless, it should be noted that the number of publications (12 and 29, for the team and collaborative studies, respectively) and the quality is good (global mean impact factor is about 4.2). Among the 12 publications, 5 are published in journals with IF ranging from 5 to 6: J Immunology, Cell Mol Life Sci, Br J Pharmacology and Mol Cell Biol, the level of the publications from the team remains fair for the field of research. Of note, the mean impact factor is much higher when taking into account the publications with contributions of the team and joining members (11 publications with an IF > 8). However, most of the high ranked papers are not related to the field of research of the proposed team.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team has already developed specific collaborations with national and international research groups (US, UK). The recruitment of high level (inter)national scientists is not yet achieved. It is noted that the participation to international congress can be improved, whereas, this remark is less valid concerning national or local conferences or symposia. This argument can be counterbalanced by the fact that nearly all the team members (past and future team) have important teaching, social or clinical activities, but remain still productive. Overall, the team has developed strong collaborative work with other teams of the present center.

- Appreciation on the scientific strategy and the project

The main project is split into 3 main aims and 5 sub-objectives/subprojects. The main remark is related to the ambitious and relatively high risk of putting together different specific fields of research. In general, the projects are well designed and described, the background is clear and the experimental approaches highly original. However, specific attention should be paid to the animal models devoted to study obesity and immune disorders (ob/ob mice versus high-fat diet induced obesity). Especially, because these parameters can strongly interfere with the phenotype, especially in term of low grade inflammation. It should be noted that BMI is not a good cut-off method to discriminate patients; different inclusion/exclusion criteria should be specified. As previously mentioned, the history of the patient will be important and should be clearly taken into account, for instance in the pregnant women. Is the obesity of the pregnant women related to the pregnancy by itself? What is the severity of the obesity? First or multiple pregnancies, is there any complication of glucose metabolism. One of the perspective works, in order to provide better insight into the mechanism would be to investigate some parts of this project in animal models. Otherwise, the findings will suffer of the correlative or associative finality of the project (human approach).

- Conclusion :

  - Summary

This is an interesting project, which will involve different partners from very different horizons. The composition of the team is somewhat ambitious with both young and more experimented PI's, more specifically given the different scientific background of the scientists joining the team. One could suspect that the team will suffer of the lack of a specialist in obesity, nevertheless, and a contrario the originality of the team also resides in part in this important heterogeneity.

  - Strengths and opportunities

The team has a "know-how" in the investigation of both pre-clinical and clinical immunology. Given the level of expertise of each collaborator (investigation of the immunity in vivo, in vitro, bioactive lipid and metabolism, animal models, pregnancy, cancer) one would suspect that the team will have in hands all the tools and ressources to facilitate the investigations. Along the same line, the association between MD's and PhD's is also a good opportunity to exchange specific points of view or strategies of interventions. Overall the projects, the technical approaches and the models are in general original and up to date.

  - Weaknesses and threats

The team is mainly represented by researchers who are also involved in numerous activities, such as teaching, clinics, or administrative responsibilities. This can probably also explain the lower international visibility among the different PI's (as shown by the relatively low level of international congress invitations, but also participations : oral/poster communication). In addition, this can jeopardize the bench work as well as the availability for young PhD students training) (labmeeting, day by day support, follow-up). Although the impact factor of several publications is relatively high (>5), it is encouraged to revise the strategy of publication in order to increase the mean impact factor and to increase publishing in the highest ranked journals, which is a feasible goal given the expertise of the team (human and animal models). When reading the program, it is not clear whether the funding supports will be applied for separately by each PI or together, in general the strategy of funding support is not clear. Finally, the lack of clear description of both animal models and human subjects, in term of obesity (criteria), can be viewed as a problem.

  - Recommendations

To improve international visibility (active participation in international meetings).

To recruit highly qualified post-docs (international attractivity) or a specialist in obesity.

To pay attention to the day by day organization and follow up of the students given the high level of teaching and administrative work.

To clearly define the animal models (DIO) of obesity and strict criteria of obese patients that will be recruited in the studies (morbidly obese, type 2 diabetic, treated or not).

To focus on specific mechanisms both in animals and humans in order to avoid descriptive studies or correlative findings in order to improve the chance to publish in high ranked journals .

4 • Appreciation team by team and/or project by project (to be pasted as many as needed)

- Title of the team and name of the team or project leader
  Epidemiology and clinical research in digestive oncology – Côme LEPAGE

Past: Team 5 BONITHON-KOPP – Future : **Team 6 LEPAGE**

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	9	10
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	5	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1.5	0.5
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	14.8	
N6: Number of Ph.D. students (Form 2.8 of the application file)	5	
N7: Number of staff members with a HDR or a similar grade	9	10

- Appreciation on the results

Team 6 previous studies resulted in a very important production in the last 4 years, with 104 papers as first, second, last or second-last authors since 2006. This production is original and covers many fields i.e. descriptive epidemiology and health care practices (≈ 40 papers with a mean IF of 4.4 – including 2 Gastroenterology), study of risk factors (4 papers with mean IF of 5.5), biostatistics (2 papers including 1 Statistics in Medicine), methodology of record linkage (18 papers), translational research (5 papers with mean IF of 6.6 – including 1 Lancet Oncology), clinical research (39 papers, mean IF of 5.2– including 1 Lancet and 3 JCO). Almost as many papers were published in lower position of authorships and/or in other fields than that of the team. Team 6 had valuable contributions to public health policy and clinical research.

One of the strengths of the team is the continuous ability in building and improving the platform constituted around the registry of digestive cancers, the registry of colorectal polyps, and the center of Randomization, Management and Analysis of clinical trials. The team obtained labels for a Registry of viral hepatitis of Côte d'Or/Doubs, for a FFCD/GERCOR Data center (INCa 2007), and for a platform of Quality of life (Ligue nationale contre le cancer 2008). Such a set of complementary tools in a same domain is impressively powerful and productive.

Team 6's partnership with local surgeons and oncologists and with international teams started 30 years ago, and increased ever since.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

No awards and invitations are indicated in the document. Team 6's studies have direct implications for public health policy and care. Team 6 constitutes large sets of data and efficiently obtained grants from public (INCa, ANR, InVS, PHRC) and associative partners (ARC, La Ligue). The team hosts one post-doc and 5 PhD students. Team 6's implication in a Master of public health contributes to its attractiveness.

- Appreciation on the scientific strategy and the project

Team 6 brings together epidemiologists, biostatisticians and clinical researchers who are really working together in a solid, coherent, long-term program. The complementary skills of the team members and the powerful tools they built are real assets.

The team conducts 2 promising original studies in primary prevention: the large-scale CIRCE study on hepatocellular cancer in cirrhosis (also carried out in China) and the multicenter AGARIC study on nutrition in colorectal cancer, which uses short-term (from erythrocytes) and long-term (from subcutaneous adipose tissue) biomarkers of FA consumption. Secondary prevention of colorectal cancer has also a rich program, including a screening study based on proteome, medico-economic studies of screening strategy in high-risk populations and studies of social disparities in early detection of cancers.

The cancer registry supports 2 important population-based evaluations of health care of colorectal cancer: one is evaluating the initial TNM staging, and one concerns the risk of relapse 10 years after the initial diagnosis. Both of them are particularly solid and will bring original information.

The methodological program continues the works conducted in the last 4-year period for the development of better models of survival, with national collaborations. There is also in depth evaluation of record linkage for incidence evaluation.

Three projects of translational research are described, all of them on prognostic factors of colon cancer. They include a study of tumor genetic and epigenetic alterations in stage II colon cancer (400 cases), a study of global DNA methylation and specific CpG island methylation (893 cases), and a study of tumoral immune characteristics and molecular tumor profile (450 CRC cases). In clinical research, one study concerns nutrition and HCC, and explores the influence of subcutaneous and visceral fat on survival. Finally, 3 clinical trials are ongoing.

- Conclusion :

Very good team, which not only constitutes high quality data sets but also makes the most of the data and develops local, national and international partnerships.

Team 6 previous studies resulted in an excellent production in the last 4 years, with 104 very good papers as first, second, last or second-last authors since 2006. One of the strength of the team is the continuous ability in building and improving the platform constituted by registries and clinical research data centers. Such a set of complementary tools in a same domain is impressively powerful and productive.

Team 6 brings together epidemiologists, biostatisticians and clinical researchers who are really working together in a solid, coherent, long-term program. The complementary skills of the team members and the powerful tools they built are real assets. The team efficiently obtained grants from public and associative partners that support the technical staff of 16 CDI.

External collaborations should be further developed for projects that include proteomics, genomics and epigenetics, for which expertise is not internally represented in the epidemiological team.

4 • Appreciation team by team and/or project by project projet (to be pasted as many as needed)

- Title of the team and name of the team or project leader

  Oxidative stress and cardiovascular risk: fundamental and clinical interplay - Catherine VERGELY

Past: LPPCE - Luc ROCHETTE - Future : **Team 7 VERGELY**

- Staff members

	LPPCE	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	14	8
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	-	-
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	1	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	-	
N6: Number of Ph.D. students (Form 2.8 of the application file)	7	
N7: Number of staff members with a HDR or a similar grade	14	10

- Appreciation on the results

This team is composed of teaching researchers, clinicians, one IR with HDR and PhD students. They contributed in the past to the development of competitive physicochemical methods for identification and quantification of reactive oxygen (ROS) and nitrogen species (RNS) and participated to the onset of 2 important clinical registers (Registre de l'Ischémie en Anesthésie en Bourgone (RIABO) and Observatoire des Infarctus de Cote d'Or (RICO)). These methods and resources are original and permitted several interesting observations concerning anthracycline-induced cardiocytotoxicity and the prognostic value of nt-proBNP for cardiogenic shock and ADMA for mortality after acute MI. They also showed in collaboration with Team 11 that high CETP rates and small HDL are associated in young patients with MI. This team also disposes of rat experimental models of metabolic syndrome and of hypertension, but the impact of these models is low on their research. The overall impression given by this Team is that they possess an efficient platform and 2 well-established cohorts which permit to host various collaborative projects, without any focused and in depth explored personal project.

This team has a very good productivity, however mostly due to the platform type of activity. Over the period 2005-2010, 65 articles signed first or last author were published in specialized journals ranging from high (9-14) IF (1 Circulation, 1 Eur Heart J, 1 Arch Int Med, 1 JACC, 1Brit Med J), medium (ATVB, Brit J Pharm, FRBM, JCEM, Am J Path, Heart) to lower (IF<5) impact. They contributed to 105 other publications, including Circulation, Eur Heart J and 4 NEJM and 2 Lancet as study investigators of clinical trials. They have a very significant activity in large public publications (14) and in writing book chapters (10).

A long term collaboration of all the members is visible, since 64/65 major publications (first or last author) are with at least 2 members of the Team and numerous, including the best ones are cosigned by several members.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

This team possesses mainly national visibillity as one of its members was invited 125 times and another one 12 times, mostly in France or Francophonie. They intensively participated into international (79, including AHA, JACC, ESC, several oral presentaions of Team members) and national meetings (94, including 12 oral presentations of Team members).

This team hosts numerous PhD students, however post-docs were scarce over the period 2006-2010 and there is no clear indication about the presence of a new post-doc in the future team 7.

This team mentioned at their oral presentation the existence of national (MESR, PHRC), regional and private fundings.

The majority of the publications of this team are in the frame of national and/or international collaborations, including multicentric clinical trials PLATO, TIMACS, registers RIABO and RICO, etc., pointing out their capacity to collaborate with foreign partners.

There is an excellent technology transfer policy, with 3 patents deposited in 2008 concerning a potential treatment of atherosclerotic plaques and the creation in 2009 of a start-up "Cohiro" dedicated to the development of these patents. This start-up was granted 2 grants from OSEO in 2008 and 2009 and is currently in incubation in Premice (incubator for new innovative companies).

- Appreciation on the scientific strategy and the project

This team proposes several projects based on association studies, however none address a mechanistic approach to uncover the molecular basis of their observations. Particularly the project concerning the overfeeding of rat pups (by reducing the size of the litter in the immediate postnatal period) and the expression of Sirt1 should be cancelled due to the severe competition in this field and the lack of appropriate tools to explore this pathway.

Although this Team possesses a very good physicochemical methodology of detection and characterisation of ROS and RNS and the excellent operational cohorts RIABO and RICO, their projects are not enough focused and frequently in fields which are too competitive to permit to compete with.

- Conclusion :

  - Strengths and opportunities

This team initiated and exploits 2 major registres RIABO and RICO permitting a high reactivity in the field of biomarkers of major metabolic diseases. This Team collaborates already with Teams 8, 10 and 11; therefore its association with LNC is strategically sound. This Team has a very good socio-economic partnership (Cohiro start-up) and 3 patents deposited during 2008 focused on the detection of atherosclerotic plaques. They have a good recruitment of PhD students and a very strong presence at major international meetings.

  - Weaknesses and threats

The choice of a relatively inexperienced team leader is not understood by the committee in light of this team's composition. The lack of post-docs is apparent, showing low attractiveness of this group for young researchers.

  - Recommendations

This team should envisage to focus their projects on the most promissing ones and to adopt in depth approaches to exploit its tools. The regroupment of this team with team 4 could possibly be considered.

4 • Appreciation team by team and/or project by project (to be pasted as many as needed)

- Title of the team and name of the team or project leader
  Pathophysiology of dyslipidemia – Bruno VERGES

Past: Team 7 – Future : **Team 8**

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	11	7
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	-	-
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	1	-
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	7.5	5.5
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	-	
N6: Number of Ph.D. students (Form 2.8 of the application file)	7	
N7: Number of staff members with a HDR or a similar grade	7	6

- Appreciation on the results

Over the past 5 years, this team has focussed its activities on diverse aspects of the pathophysiology of dyslipidemia in diabetes; the key experimental approaches have involved in vivo kinetic studies of plasma lipoprotein production, turnover and catabolism using stable isotope-labelled precursors of lipid and protein components, assessment of hepatic fat content by imaging technologies, immunoassay of systemic biomarkers of adipose tissue metabolism and insulin resistance, SNP analyses of target genes, and in vitro assays of lipoprotein functionality using rabbit aortic rings. The principal original contributions concern (1) the demonstration that adiponectin is a negative correlate of HDL-apoAI metabolism in type 2 diabetic (T2D) subjects, indicating the direct implication of this adipokine in HDL metabolism, (2) the development of validated imaging techniques for mapping hepatic fat content, a frequent characteristic of metabolic diseases, (3) the lack of relationship between liver fat content and carotid intima-thickness in T2D, (4) the variable association between liver fat and plasma triglyceride levels as a function of a single SNP (rs738409) in the adiponutrin gene, and (5) the vasodilatory activity of HDL is attenuated in both type 1 and type 2 diabetes. Past activities benefitted substantially from a strong clinical interface, facilitating in vivo evaluation of the pharmacotherapeutic impact of rosuvastatin, of an inhibitor of the cannabinoid receptor 1, and glitazones on the metabolism of atherogenic and non-atherogenic lipoproteins in T2D subjects. Some 97 publications in peer-reviewed journals have been produced, of which 21 have IF > 5.0. The group leader contributed significantly to the discovery that apoAV is a major component of the lipolytic system in man (JCI 2005). Members of the team have frequently communicated their findings at national and international levels.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The Team leader has an established international reputation in his domain of expertise; he is equally an accomplished diabetologist and Head of Department. In addition, several members of the Team have major clinical activities. By virtue of its pharmacotherapeutic studies, this team has successfully raised research funding from industry and from the public sector (CHU Dijon, University of Bourgogne). The team's research programme and expertise are attractive to foreign partners as judged by their participation in international and national multi-center clinical studies.

The management of this team can be judged to be satisfactory given its scientific production. However its capacity to train and mentor young scientific and clinical investigators remains to be proven. Team members have major teaching responsibilities in the University and Medical School. With respect to structuration of research at the local level, the number of completed doctoral theses over the period 2005-2010 is not clearly indicated.

- Appreciation on the scientific strategy and the project

The research project largely represents the further development of ongoing studies with similar technological and clinical approaches and infrastructure, and is focussed on the study of the pathophysiology of diabetic dyslipidemia and the role of insulin resistance and hepatic fat content. The component subprojects are focussed on: (1) the relationship of hyperinsulinemia with or without insulinoresistance to hepatic VLDL overproduction in T2D and to liver fat in human subjects, (2) the relationship between the degree of hepatic steatosis and the in vivo kinetics of triglycerides and apoB lipoproteins, with nutritional state (fasting/non-fasting) and free fatty acid infusion as variables in diabetic subjects, (3) the relationship between plasma adiponectin level and lipoprotein metabolism in vivo, (4) the effect of adiponectin on lipid metabolism in vitro in liver explants from mice on lipid and fatty acid metabolism, (5) the vasorelaxant capacity of HDL from type I and type 2 diabetic subjects, and the roles of NO and of HDL glycooxidation in such activity, (6) the effect of HDL from diabetic subjects to modulate adiponectin production by adipose tissue (subcutaneous and visceral origin). The unifying working hypothesis linking these disparate objectives remains to be identified. The clinical dimensions of this project are however entirely feasible given the privileged and dynamic clinical interface from which this team benefits. Finally, the project features a significant pharmacotherapeutic component, involving in vivo turnover studies of the effects of a statin, of glitazones and of endocannabinoid receptor antagonists, and of a GLP1 inhibitor on the metabolism of triglyceride –rich lipoproteins and HDL. The scientific and clinical prioritisation of these studies requires further consideration.

- Conclusion :

Overall, this team possesses a key technology appropriate to in vivo studies of lipoprotein metabolism in the dyslipidemia of diabetes and metabolic disease and to its pharmacological modulation. Furthermore, the team is highly clinically qualified in the diabetes field with excellent facilities for in vivo experimentation in human subjects. However the research project lacks coherence and a unifying working hypothesis; its major goals require clear identification. The project is equally devoid of an experimental component focussed on intravascular lipoprotein remodelling; such a component would facilitate insight into the mechanisms underlying HDL dysfunction in type 2 diabetes. Major opportunities for cutting edge research are presently appearing for this team given new knowledge of molecular crosstalk between regulation of lipid and glucose metabolism in insulin resistant states. The originality of the preclinical studies is questionable and is not within the area of competence of the team.

To ensure its positive evolution, the team must develop a strategic plan for the training and integration of young scientific and clinical investigators. In this way the team could be consolidated by recruitment of at least one tenured research scientist or clinician. Equally a clear strategy for continued research funding should be defined.

Given the current pandemic of obesity, diabetes and premature cardiovascular disease, it is critical to emphasise the immediate relevance of the programme of Team 8 to public health.

4 • Appreciation team by team and/or project by project (to be pasted as many as needed)

- Title of the team and name of the team or project leader

  Sensing and metabolism of lipids and dietary contaminants in the oro-intestinal tract: effects on health and feeding behaviour – Philippe BESNARD

Past: Team 6 – Future : **Team 9**

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4	8
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	-	-
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	1	-
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	3.5
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0.5	
N6: Number of Ph.D. students (Form 2.8 of the application file)	4	
N7: Number of staff members with a HDR or a similar grade	2	4

- Appreciation on the results

This team is focused on lipid sensing in the oral cavity and gut, and the effect on feeding behaviour and metabolism. This is a highly topical area of research as it may highlight new therapeutic avenues for obesity, diabetes and metabolic disorders.

The team was previously small, originally comprising only 1 Pr, 2 Ass Pr and 1 tech, increasing by 1 E in 2009. Despite their small size, the team made the important discovery that the receptor CD36 is implicated in fat taste – a finding that received international recognition, as evidenced by the high impact original publications (e.g. JCI) and reviews (e.g. Prog Lipid Res) that resulted. Other findings from the team were published in relatively good journals for the field, such as Gut and FASEB J. Publications from the group fell after the initial 2006 discovery but are now increasing again.

Two additional groups will join the team in this round, both with moderate publication records (e.g. J Autoimmun, JCEM, Prog Lipid Res). The joining group of Khan already has a long history of publishing with Besnard, so this is likely to be a stable partnership.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team leader, P Besnard, has been invited to speak at 6 international meetings between 2006 and 2010 (Germany, Switzerland, Spain), plus 1-3 national meetings per year. His work is recognized by 3 national awards. He is the coordinator of several competitive collaborative grants. Of the 2 joining groups, Khan has been an invited speaker at a number of international meetings, and Chagnon has presented work at national meetings. All have established national and international collaborations.

- Appreciation on the scientific strategy and the project

The team has presented a strong proposal for the next 4 years of research, divided into 4 work packages, all of which are scientifically strong and feasible. The proposals use state of the art technologies, including immunomagnetic purification of specific cell populations, transcriptomics, genetically modified mouse models, murine phenotyping and studies of human physiology and metabolism. The aim is to investigate the mechanisms of lipid triggered signaling in taste cells and the intestinal tract, and the effect on whole body metabolism (in animal models and humans) and behaviour (e.g. food preference). These are original cutting edge projects, with the potential to alter how we view the link between the fat content of foods and its consequence on whole body metabolism.

- Conclusion :

  - Summary

This is a strong focused research team with a history of novel internationally recognised findings. It comprises investigators with a wide range of technical expertise, ranging from single cell functional analysis to whole body metabolism

  - Strengths and opportunities

The bringing together of basic cell biology, mouse phenotyping / behaviour, and human studies provides opportunities to translate findings in both directions – from cell biology to human physiology and vice versa. The use of mouse models with deletion of specific genes provides a route to evaluate the physiological importance of candidate signalling pathways in vivo.

The team has a good history of producing influential publications, particulary considering its previous small size.

The team leader has received awards and international recognition.

The program includes a study of the toxic effects of food packaging contaminants. This is a high risk, high potential benefit project, which could impact on the behaviour of the food industry.

The project includes a screening platform used by the food industry.

The team have network grants for studying fat taste and metabolism in humans.

  - Weaknesses and threats

Publications from the group fell slightly after the initial 2006 publications but are currently increasing with the establishment of more collaborations.

The new structure of the group will incorporate 2 new teams who will need to work together to achieve a common goal. However, they have a history of working and publishing together and presented a good interactive program.

  - Recommendations

This proposal incorporates strong research and innovation, at multiple systems levels. The outcomes are likely to have global impact on nutrition and health. The association with the Packtox platform opportunities to identify novel toxic food contaminants. The findings from this project could be fed positively into the rest of the research program.

4 • Appreciation team by team and/or project by project (to be pasted as many as needed)

- Title of the team and name of the team or project leader
  Intracellular dynamic of fatty acids and inflammation - Gérard LIZARD

Past: Team 9 LATRUFFE – Future: **Team 10 LIZARD**

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	11	8
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	3	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.8 of the application file)	8	
N7: Number of staff members with a HDR or a similar grade	9	6

- Appreciation on the results

This team has addressed different aspects of abnormalities of the intracellular dynamics of fatty acids, focusing on the role of peroxisomes in very-long chain fatty acid oxidation in relation to the etiology of different leukodystrophies. X-ALD represents the most frequent peroxisomal disorder with very limited therapeutic options. The team has carried out original and important work towards understanding the molecular basis of X-ALD, namely i) the analysis of the different ABC transporters in the peroxisomal membrane resulting in the identification of inducers of the ALDP homolog ALDRP with potential therapeutic implications; ii) studies on the role of ACOX1 in relation to pseudo neonatal-ALD; iii) the analysis of the mechanisms of demyelination using novel in vitro models and providing the potential to search for biomarkers. However, some subprojects were less successful. Thus, the analysis of L-carnitine dependent enzymes (COT), and the analysis of peroxisomal thiolase B did not result in major outcomes and publications. A different project was carried out regarding the effects of resveratrol in the nutritional prevention of cancer. The project will continue with some reorientation towards mitochondrial function. Team#10 presents a publication list with limited quality. Only 6 papers have an IF>5, some principal investigators have an insufficient publication record (either very low numbers or low IF). Obviously, some projects could not be run very successfully, reflected by the low number of high-quality papers. The number of thesis output is appropriate and correlates to the scientific activity of the team and the unit.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Profs Latruffe and Lizard have been invited to a substantial number of conferences and international meetings and are on the editorial Boards of Scientific Journals. Information on the other team members and of any awards is not available. The team has successfully applied to competitive grants and receives funding by industry and several national and local agencies.

- Appreciation on the scientific strategy and the project

The team presents a partly coherent research program,that addresses a number of questions related to the molecular basis of peroxisomal leukodystrophies. In aim#1, they suggest 5 workpackages that are tightly linked and focus on several peroxisomal target proteins (ABCD transporters, COT, ACOX), the mechanisms of demyelination and the identification of novel therapeutic targets. Aim#1 describes the most extensive part of the novel research strategy and, overall, is a feasible and promising approach.This is further extended by aim#2, which addresses potential treatment of leukodystrophies, and the definition of novel biomarkers of demyelination. This part is of interest, but the chosen strategy needs to be redefined. In aim#3 a strategy is presented to improve mitochondrial fatty acid metabolism by using resveratrol. Obviously, aim#3 is not directly related to aims#1 and #2, and this aim needs re-organization. Further, the planned studies on L-carnitine and COT do not show any progress compared to the previous period. No papers were published by the PI regarding COT and the preliminary results are not sufficient. This project needs to be restructured or deleted from the work program.

- Conclusion :

  - Summary

Team#10 presents a mostly solid working report with several key findings in the field of peroxisomal diseases and has proven expertise and international reputation in the field of leukodystrophies and its molecular basis. The group has partly conducted good work and presents a logic continuation for future original work in the field. Several new projects are good and promising, the search for biomarkers of demyelination is important and timely, but the presented strategy needs modification. Several additional weak points (see below) were identified and the publication strategy needs to be improved.

  - Strengths and opportunities

The major strength of this project is the unique assembly of researchers (both clinicians and basic scientists) with expertise in the field of peroxisomal disorders and specifically X-ALD. This rare disease is far from being understood and the large spectrum of phenotypes and clinical appearance needs intensive research, specifically for developing novel therapies for this fatal disease. This research is only possible in a network of specialists (both local and national/international) as presented here. The team has a great opportunity to identify novel targets for treatment and biomarkers for better prevention of ALD.

  - Weaknesses and threats

The team needs to improve its publication strategies and more high-impact factor journals should be addressed. The output of the PIs may need a better quality control and several projects are not novel and need to be re-defined. Participation in International Projects needs to be reinforced and this also applies to the recruitment of scientists from abroad. The project should be focused on the original and innovative research. The resveratrol project is not sufficiently innovative, deviates from the major goals and should be removed.

  - Recommendations

This team is an important contribution to the Research Center and provides unique expertise to the aspects of intracellular dynamics of fatty acids with emphasis on the peroxisomes and related rare diseases. The project definitely needs reorganization and focusing.

4 • Appreciation team by team and/or project by project projet (to be pasted as many as needed)

- Title of the team and name of the team or project leader
  Lipid transfer proteins and lipoprotein metabolism – Laurent LAGROST

Past: Team 8 – Future: **Team 11**

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	4
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	2	-
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	2	
N6: Number of Ph.D. students (Form 2.8 of the application file)	3	
N7: Number of staff members with a HDR or a similar grade	6	6

- Appreciation on the results

This team directed by Dr. Laurent LAGROST foccused its work on the pleiotropic role of plasma lipid transfer proteins in lipoprotein metabolism and has accomplished very significant work in this field. Also, additional and innovative work on nuclear receptor pathways in 'Reverse Cholesterol Transport' (RCT) has been succesfully conducted and offers promising perspectives. Most of these studies have been supported by molecular and cellular approaches, animal models and clinical data

The scientific production of the team is very important: 66 publications in the period 2005-2010, 58 % internal to the team. Pulications (37) are mainly in mid/high-ranking journals: 19% with an I.F between 2-4, 32% between 4-6, 46 % between 6-10 and 3% > 10, with some articles being published in the best specialty journals: J Am Coll Cardiol. (1), Circ. Res. (1), ATVB (7), J Lipid Res. (5), Faseb J (2). Collaborative publications (29) include Nature (1) and Circulation (1). 2 patents have been issued directly from current projects of the team. Significant activity in writing book chapter and reviews in French (6).

The new configuration of the team consists of 4 permanent researchers (2 DR and 2 CR), 5 PU/MCU-PH, 1 Post-doc, 3 technicians/Engineers (1 permanent and 2 with contracts) and 5 PhD students. A long term collaboration of all the members is visible since all internal publications are with at least 2 team members and numerous are cosigned by several members.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Participation to conferences and meetings is good with 18 invitations and 1 scientific communication with proceedings in international (11), and national (8) meetings, and 6 poster presentations in international (1) and national (5) meetings

The new team will be reinforced by the arrival of 3 researchers: Dr M. ISHIBASHI (Cardiologist, MD, PhD), Dr S. MANDARD (MCU) and Dr T. GAUTIER (CR1). These new permanent researchers, together with several PhD students (5) confirm the attractiveness of the team.

The team efficiently obtains regular fundings: Regional (regional Council of Burdundy), National (1 ANR grant as coordinator -2006-2010- and 1 'Translational Research Program' of INSERM and DHOS) or International (participation in 1 European contract) fundings. The team also raised fundings from Medical and Scientific foundations and from research contracts with industrial partners.

There are numerous national and international collaborations: J. Davignon and L. Bernier (Montreal, Canada), Pr F. Kuipers and U. Tietge (Groningen, The Netherlands), XC Jiang (SUNY Health Center, Brooklyn, New York), Dr M. Assem (University of Iowa) and Dr D. Moore (Baylor College of Medicine, Houston), Dr LM Houdebine and Dr G Jolivet (INRA, Jouy-en-josas). There are collaborations with team 1, 3, 4, 5, 6, 7, 8 and 9 within the center.

2 patents were deposited in 2010 and are directly issued from current projects of the team.

- Appreciation on the scientific strategy and the project

The project is the continuation of the previous work. All aims focus on the exploration of the physiological relevance of previous targets identified by the team. The experimental approaches are very good with appropriate and original animal models and human populations. Each aim appears well suited, with "proof of concept" studies. In summary, the team's expertise in this field and excellent experimental tools and approaches is a clear advantage for the feasability of the projects.

The team has shown a strong ability to obtain regular regional, national and international fundings, from Fundations and private sector. All PhD students have research funding from the MESR or hospital.

The development of new animal models and therapeutical tools for improving HDL functions is original and promising. This should allow the group to produce an outstanding level of publications.

- Conclusion :

  - Summary

Very strong world-class leading group which helps keeping France in a competitive position in the field of lipoprotein metabolism related to atherosclerosis and other pleiotropic functions.

  - Strengths and opportunities

Outstanding leader international by reknown; Excellent program and project management; Investigations are performed using various approaches; Synergy between the different projects; Strong collaborative partnership with foreign and French groups; Numerous collaborations with other teams within the institute.

  - Weaknesses and threats

Contribution to conferences is good but does not always reflect the excellent publication level.

  - Recommendations

The project is excellent and feasible. It is largely oriented to translational research and "proof of concept studies", in line with previous observations made by the team and we recommend not to forget fundamental basic science studies. Team members should apply more often to present data in international conferences to increase the international visibility of the team and to facilitate recruitement from abroad.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
LIPIDES, NUTRITION, CANCER	**A**	**B**	**A**	**A**	**A**
SENSING AND METABOLISM OF LIPIDS AND DIETARY CONTAMINANTS IN THE ORO-INTESTINAL TRACT [LAGROST-BESNARD]	A	A	Non noté	A+	A
NITRIC OXIDE AND CANCER [LAGROST-BETTAIEB]	A	B	Non noté	B	B
OBESITY AND IMMUNITY [LAGROST-BONNOTTE]	B	B	Non noté	A	B
GENE REGULATION IN HEMATOPOIESIS AND LEUKEMOGENESIS [LAGROST-DELVA]	A	B	Non noté	A	A
HEATH SHOCK PROTEINS : CELL DEATH, CELL DIFFERENTIATION AND TUMORIGENIC PROPERTIES [LAGROST-GARRIDO]	A+	A+	Non noté	A+	A+
CHEMOTHERAPY, LIPID METBOLISM AND ANTI-TUMORAL IMMUNE RESPONSE [LAGROST-GHIRINGHELLI]	A+	A+	Non noté	A	A+
LIPID TRANSFER PTOTEINS AND LIPOPROTEIN METABOLISM [LAGROST-LAGROST]	A	A	Non noté	A+	A
EPIDEMIOLOGY AND CLINICAL RESEARCH IN DIGESTIVE ONCOLOGY [LAGROST-LEPAGE]	A	A	Non noté	A	A
INTRACELLULAR DYNAMIC OF FATTY ACIDS AND INFLAMMATION [LAGROST-LIZARD]	B	B	Non noté	B	B
OXIDATIVE STRESS AND CARDIOVASCULAR RISK: FUNDAMENTAL AND CLINICAL INTERPLAY [LAGROST-VERGELY]	A	B	Non noté	B	B
PATHOPHYSIOLOGY OF DYSLIPIDEMIA [LAGROST-VERGES]	A	A	Non noté	A	A

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	**42**	**5**	**20**	**26**	**36**	**59**	**5**	**17**	**29**	**239**
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

*** les résultats SVE2 ne sont pas définitifs au 06/05/2011.**

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

- **SVE1 Biologie, santé**
  - **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
  - **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
  - **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
  - **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
  - **SVE1_LS5 Neurosciences**
  - **SVE1_LS6 Immunologie, Infectiologie**
  - **SVE1_LS7 Recherche clinique, Santé publique**
- **SVE2 Ecologie, environnement**
  - **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
  - **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
  - **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

UNIVERSITÉ DE BOURGOGNE

La Présidente

à

Monsieur Pierre GLORIEUX
AERES
Directeur de la section des unités de recherche
20 rue Vivienne
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Dossier suivi par :
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Responsable du Pôle Recherche
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Dijon, le 31 mars 2011

Objet : Evaluation AERES - S2UR120001814 - Lipides, Nutrition, Cancer (LNC) - 0211237F

Monsieur le Directeur,

Je vous remercie de l'envoi du rapport d'évaluation comportant un avis globalement très positif sur le laboratoire « Lipides Nutrition Cancer » qui associe l'université de Bourgogne et l'INSERM et vous prie de bien vouloir trouver ci-après la réponse de son Directeur, Monsieur Laurent Lagrost.

Je tiens par ailleurs à souligner le travail de restructuration conduit par le laboratoire « Lipides Nutrition Cancer » durant le présent contrat d'établissement afin de promouvoir l'excellence scientifique et la visibilité internationale des recherches qu'il conduit. Ce laboratoire s'est parfaitement intégré au sein du campus dijonnais en nouant des relations fructueuses avec les autres acteurs scientifiques ainsi qu'avec les établissements de santé favorisant ainsi la recherche translationnelle.

Je tiens enfin à réaffirmer le soutien de l'université de Bourgogne à cette unité de recherche qui occupe une place prépondérante dans un des pôles d'excellence de notre établissement au travers notamment des projets « Investissements d'Avenir » du PRES Bourgogne Franche-Comté.

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

UNIVERSITÉ DE BOURGOGNE

Sophie BÉJEAN

Centre de Recherche « Lipides, Nutrition, Cancer »

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To whom it may concern

As director of Inserm Research Center UMR866 at the University of Burgundy (Dijon), I thank the AERES committee members very much for their time and effort in evaluating our 2012-2015 proposal.

My Colleagues and I read the draft report, which was recently sent to us, very carefully and all of the analyses, comments and advice were much appreciated by all of us. They will be of significant help in strengthening our research plans and general organization.

The information was extremely clear and I have no comments to add or changes to make.

Sincerely yours

Dijon, March 30th 2011

Laurent LAGROST
Directeur du Centre de Recherche Inserm UMR 866