HCERES

High Council for the Evaluation of Research and Higher Education

Research units

HCERES report on research unit:

Biochemistry of the peroxisome, Inflammation and Lipid metabolism

Bio-PeroxIL

Under the supervision of the following institutions and research bodies:

Université de Bourgogne - UB

Evaluation Campaign 2015-2016 (Group B)

Evaluation report

This report is the sole result of evaluation by the expert committee, the composition of which is specified below.

The assessments contained herein are the expression of an independent and collegial reviewing by the committee.

Unit name:	Biochemistry of the peroxisome, Inflammation and Lipid metabolism
Unit acronym:	Bio-peroxIL
Label requested:	EA
Current number:	EA 7270
Name of Director (2015-2016):	Mr Gerard LIZARD
Name of Project Leader (2017-2021):	Mr Gerard LIZARD

Expert committee members

Chair:	Mr Marc POIROT, Inserm, Toulouse
Experts:	Ms Liliane BERTI, University of Corse (CNU representative)
	Mr Marc ENGELEN, Academisch Medisch Centrum, Amsterdam, The Netherlands
	Mr Marc FRANSEN, University of Leuven, Belgium
Scientific delegate representing the HCERES:	
	Mr Jean GIRARD
Representative of supervising institutions and bodies:	
	Mr Jean GUZZO, University of Burgundy
Head of Doctoral School:	
	Mr Thierry RIGAUD, ED n°554 « Environnements-Santé »

1 • Introduction

History and geographical location of the unit

The EA 7270 unit was created on the January 1st 2012 and is headed by Mr Gerard LIZARD. This unit is an extension of the team n°9 ("Metabolic and Nutritional Biochemistry"), previously directed by Mr Norbert LATRUFFE, from the Inserm center U 866. The unit is located at the faculty of sciences "Gabriel" of Dijon. The unit is composed of about 50 people including 14 permanent researchers/teachers.

Management unit

The unit will be managed by the current director Mr Gerard LIZARD. A management committee composed of the four theme leaders will decide on the progression and on the strategic orientation of the unit four times a year.

HCERES nomenclature

SVE1_LS1 Biologie moléculaire et structurale, biochimie

Scientific domains

The scientific domains are related to the study of peroxisome organelles in the context of lipid metabolism, mainly in the pathogenesis of peroxisomal disorders, secondly on neurodegenerative diseases. The unit covers basic research as well as pharmacological and clinical aspects in these fields. The unit proposes the exploration of novel lipid biomarkers of the pathogenesis as well as the identification of new natural inhibitors of new pharmacological targets in these diseases.

Unit workforce

Unit workforce	Number on 30/06/2015	Number on 01/01/2017
N1: Permanent professors and similar positions	8	7
N2: Permanent researchers from Institutions and similar positions	1	1
N3: Other permanent staff (technicians and administrative personnel)	4	6
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (technicians and administrative personnel)	4	
N7: PhD students	5	
TOTAL N1 to N7	**23**	
Qualified research supervisors (HDR) or similar positions	6	

Unit record	From 01/01/2010 to 30/06/2015
PhD theses defended	8
Postdoctoral scientists having spent at least 12 months in the unit	
Number of Research Supervisor Qualifications (HDR) obtained during the period	

2 • Overall assessment of the unit

Introduction

The unit is one of the only few french units studying the organelle peroxisome in collaboration with national and international networks. The research of the unit is composed of both fundamental and clinical approaches. With the creation of the EA 7270, and according to the remarks of the previous AERES expert committee, the theme was focused on lipids with regards to peroxisomal metabolism in the context of peroxisomal disorders.

The unit is structured in 4 themes. It includes 14 members including 1 CR Inserm, 4 professors, 1 emeritus professor, 4 associate professors (with a total of 6 HDR), 1 research engineer, 1 research technician, and 2 technical assistants (including 1 at 20%).

The molecular origin of peroxisomal disorders with neurological involvement is the federating topic of the four themes, in which different though complementary activities are developed:

- theme 1: biochemical and structural aspects of peroxisomal ABC transporters;

- theme 2: roles of the peroxisomal enzyme ACOX-1 in inflammation and oxidation;

- theme 3: impact of the peroxisomal enzyme COT in the peroxisomal ß-oxidation of fatty acids;

- theme 4: relationship between peroxisome-neurolipotoxicity and lipid biomarkers of neurodegeneration.

To improve its research activity, the EA 7270 unit recruited a research technician and an associate professor in 2011. An associate professor of the unit was promoted to full professorship in 2012. The scientific production is very good for a small unit and proves its exceptional dynamism.

By focusing its research program on the peroxisome, the unit is very well interfaced with the local and regional actors. The structuration of the unit in 4 themes is relevant. Moreover, the unit is decidedly positioned in the field of academic fundamental research and strongly interacts with clinical institutions. The unit is also invested massively in training through research, which is reflected by the large number of students of various levels (junior high/high-school, vocational, bachelor, master, PhD and post-doctoral) hosted in the laboratory. This strong implication in training through research is explained by the large proportion of teacher to researchers in the unit (70%) from the UFR “Science Vie, Terre et Environment”. The members of EA 7270 are also strongly involved, at various levels, in the life of the university (Boards, Commissions, management of teacher training). In addition, the members of the unit are also very active in interacting with the socio-economic and cultural environment.

Global assessment of the unit

The team is composed of a laboratory director who heads a team of 14 permanent position persons, 9 of them being assistant professors or professors. The team has been joined by neurologists, which will give new opportunities of translational research, on peroxisomal defects-related diseases that include neurodegenerative diseases, and of fund raising for the unit. The laboratory has published a significant number of good publications in its field of expertise and had the opportunity to write review articles, present its work in international meetings as well as in social and economical instances.

Strengths and opportunities in the context

This unit has developed an original research on “peroxisomes” and importantly, neurologists from Dijon’s Hospital will join the unit to develop translational research programs on peroxisomal defects-related neurological diseases. This unit shows complementary skills between groups, establishing a good cohesion. The unit shows a very good synergy between education and research, and a very good dynamism in the participation in projects promoting international networks of experts in lipid metabolism. The unit has acquired high performance equipment.

Weaknesses and threats in the context

The unit is not attached to a national research organism, which makes it more difficult to obtain grants and private contracts on the peroxisome theme, and interactions with clinical teams were limited.

Recommendations

The expert committee recommends measures to increase the stability of this group of researchers of remarkable dynamism. We recommend that the unit continues to work on lipid metabolism in peroxisomal disorders, which will improve the scientific identity of the laboratory at the national and international levels, and, to this end highly recommends a strategic analysis of research complementarities and funding. The expert committee strongly recommends that the unit try to achieve a better balance between research and scholarly activities.

3 • Detailed assessments

Assessment of scientific quality and outputs

EA 7270 developed a research program focused on links between peroxisomal lipid metabolism, oxidative stress and inflammation in the context of neurodegenerative demyelinating peroxisomal disorders (X-linked adrenoleukodystrophy - X-ALD - and the peroxisomal acyl-coenzyme A oxidase 1 - ACOX1 - deficiency). The unit's field of investigation has recently been extended to other neurodegenerative diseases in which the role of the peroxisome is suspected (Alzheimer disease, multiple sclerosis). In these diseases, the unit's research has a two-fold aim: on one hand, to understand the underlying molecular mechanisms, so that progression of the disease can be better followed thanks to the identification of specific biomarkers; and, on the other hand, to identify new therapeutic approaches, thanks to the screening of natural or synthetic molecules, in order to improve the treatment of these neurodegenerative diseases. The aim of the unit members is consistently to better understand the role of the peroxisome, its impact on inflammation and on RedOx balance, and its involvement in lipotoxicity within nerve cells, glial cells and microglia. To achieve this, the unit will develop new approaches and new in vitro cellular tools. With the reconfiguration of the unit, they will also conduct translational research to generate knowledge that will lead to the development or improvement of therapies for the diseases studied in the laboratory: X-ALD, ACOX1 deficiency, multiple sclerosis, Alzheimer disease, Parkinson disease. Some of these diseases, in particular multiple sclerosis, are familiar to the clinicians who joined their unit. To achieve this, the laboratory has implemented two approaches: the identification of molecules of pharmacological interest and the search for specific biomarkers of these diseases. This new orientation seems very relevant.

The unit has improved the understanding of the biological function of peroxisomes with regard to lipid transport and metabolism. Mainly, they have patented a lipid signature allowing the detection of peroxisome-related diseases.

With the creation of a COMUE "COMmunautés d'Universités et d'Établissements" between the University of Burgundy and the University of Franche-Comté, the unit's interactions with the CHU of Besançon (Neurology Department, CMRR) will be reinforced. In addition, the orientation of the laboratory towards neurodegenerative diseases will reinforce its local interactions with the Inserm unit 1093 of Dijon (Cognition, Action, and Sensorimotor Plasticity), the Geriatric Medicine Department of the CHU, and teams from the "Centre des Sciences du Goût et de l'Alimentation" (CNRS/INRA).

The unit presents a very good balance of scientific publications: 72 publications (51 as 1rst or senior author) over the 2010-2015 period for 9 EC (4.5 ETP) and 1 CR Inserm, which corresponds to 2.67 research publications/ETP/year. Lab members also published 25 reviews (24 as 1rst or senior author), 5 letters (as 1rst or senior author), 4 editorials (as 1^{rst} or senior author), and 10 books and contribution to books (as 1rst or senior author). This corresponds to a mean of 4.2 publications/ETP/year. The highest impact factor achieved in publications specific to the laboratory was 7.517, and 38% of the publications had an IF>4. 50 to 56% of the articles are published in journals belonging to the highest quartile of their specialty.

The number of citations was not documented, but the H factor of the PI is 37 (ISI Web of Science 2015) showing an excellent citation track. The unit has published in very good international journals in different fields of specialty that can be linked to their activity, such as biochemistry (J Biol Chem, Biochimie, BBRC), lipids (Chem Phys Lipids, Steroids, BBA-MCL), and generalist (Plos ONE) journals. Importantly, this quality is seriously improved by the neurologists who will join the unit and recently contributed to publications in high impact journals such as NEJM and Lancet.

A productive collaboration with Ireland (University of Cork) and Tunisia (the Pasteur institute of Tunis) led to PhD co-tutorships, joint publications and patents.

Short appreciation on this criterion

The scientific production and the quality of the unit are very good. Independently of this publication criterion, Bio-PeroxIL develops a research line with original approaches.

Assessment of the unit academic reputation and appeal

The unit actively participates in national academic (ANR) and industrial projects. In addition, the unit also participated in a European program and in bilateral collaborations ("Programme Hubert Curien", PHC). Finally, the unit also developed several collaborations with private companies (THEA and Pierre Fabre drug companies, the Burgundy Wine Board - BIVB, the private health insurance company APICIL, the applied research lab Kirial/Spiral, the Nutraservio lab).

The unit has a very good to excellent interfacing at the regional level and in national networks. Among the different interventions of members of the unit in the organization of networks on peroxisomal diseases and peroxisome biology, it should be noted that the PI is one of the two founders of the European Network on Oxysterol Research (http://oxysterols.com/; ENOR), which initiated connections between European groups working on oxysterols. This network has attracted teams in a broad range of disciplines ranging from chemistry to clinical studies. This initiative led to the organization of annual meetings throughout European countries and had a strong impact on the field of oxysterols, thereby significantly improving the number and quality of publications of the members.

Several teachers and researchers have been hosted by the laboratory. They came from Morocco, Algeria, Ireland and Tunisia. They have also hosted 7 Tunisian, Algerian and Moroccan doctoral students.

The unit is well recognized in the field, as evidenced by the successful organization of international symposia and workshops, by the two awards obtained, and the involvement in multiple developmental and collaborative programs (Erasmus, PHC).

The activities of the unit on the definition of the biological and pharmacological properties of natural or synthetic molecules were awarded twice (2011, 16th World Congress on Advances in Oncology; 2011, Fondation APICIL).

Members of the unit were invited to act as guest editors to publish special issues of internationally recognized journals (Chemistry and Physic of Lipids, Current Drug Metabolism, Biochimie, Steroids). The neurologists who will join the unit have contributed to publications in high IF journals (Lancet, NEJM, etc.). More than 50% of the scientific output of the lab (excluding publications from the clinicians) is published in journals ranked in the first quartile of their category (according to the ISI web of science classification).

The unit is involved in the organization of an annual international meeting such as the ENOR in which first-ranked European teams and more generally international teams (including key opinion leaders in the top 10) are present. The PI was founder of the ENOR and hosted the meeting in Dijon once in 2013. The unit also organized two other meetings: one on peroxisomes (OEPM, 2012), and another one on natural antioxidants (NutriOx, 2013). In addition, the unit is involved in network management: European Adrenomyeloneuropathy Board, NutriOx, European Network on Oxysterol Research, PHC Volubilis and Ulysses, Association Méditerranéenne Francophone d'Imagerie et Cytométrie.

Unit members were invited as speakers to give lectures or oral communications in international meetings (30 times) and 18 national or regional meetings.

Members of the unit reviewed articles to an average of 7 articles/month in international journals with IF ranked between 2 to 15.

Short appreciation on this criterion

Member of the unit gave numerous invited conferences of reviews demonstrating their international visibility. The scientific production is noteworthy, taken into account the involvement of the unit members in teaching activities, this a very good unit.

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

It is noteworthy that the unit filed 2 patents for which very good intermediary reports of research were obtained. These patents claim the use of several long-chain fatty acids as selective markers of peroxisome-related neurodegenerative diseases.

Patented methods of dosage will be easily transferred to other laboratories and clinical laboratories of analytical biology. Cellular tools that will be developed by the unit should be patentable.

The unit will move on to the use of the Crispr/Cas9 methodology to invalidate gene expression in cell lines in order to produce research tools. Oxysterols recently appeared as cholesterol metabolites of growing physio-pathological importance in several diseases such as neuro-degenerative diseases, cardiovascular diseases, viral infection and cancers.

The unit has produced a didactic book for students, 10 book chapters, and 25 reviews in peer-reviewed journals, thereby establishing an excellent contribution to knowledge dissemination. Members of the unit contribute to interviews diffused by national and regional TVs or radios. They are involved in training in bioinformatics and flow cytometry at the doctoral school and in Morocco and Tunisia. As professors at the University of Burgundy, they are also involved in teaching organization.

Partnerships with chemists from the University of Lorraine and with academic labs from the Maghreb countries have resulted in resources for the development of pharmacological modulators of peroxisomal ATP transporters of synthetic and natural origin.

Short appreciation on this criterion

The unit has a very good activity, which led to the filing of two patents. It should also be noted that the existence of a good partnership with excellent chemists (University of Loraine) and foreign groups provided the unit with opportunities to explore the potency of natural substance on relevant targets.

Assessment of the unit organisation and life

The four groups are complementary and work on different aspects of the same theme, which is focused on peroxisomes, their function, their pharmacological targeting, and their relationship with neurological diseases.

The unit has its own equipment and has access to technical resources to perform its research activities.

Two lab meetings are scheduled on a weekly basis: one for presenting and discussing results, and another one for critical analyses of data from the recent literature (journal club).

The unit has scheduled weekly - and monthly - based lab meetings dedicated to discuss scientific results, budget, recruitment, hosting of students, and acquisition of material.

The unit has a high visibility with an up-to-date web site (http://bioperoxil.u-bourgogne.fr/) hosted by the University of Burgundy. The web site is well detailed on all aspect of the unit's life and environment.

All the staff members (permanent and temporary) are trained for hygiene and safety. The laboratory is well equipped. One of the technical staff members obtained the degree after having followed the regulatory training for radioprotection, and permanent staff members (engineers and technicians) handle the maintenance of the equipments.

Short appreciation on this criterion

The unit is well equipped and has an access to technical resources to implement its research plan; moreover the unit fulfils the rules of regulatory health and safety in term of equipments, personal skills and formation for newcomers. The unit is well organized and administered. The organization and visibility of the unit is very good to excellent.

Assessment of the unit involvement in training through research

The unit hosts first, second and third cycle students. The unit is involved in the Doctoral School "environment and Health" (ED n°554, "Environnements-Santé"). Based on the interviews of students that were conducted by expert committee members, it was found that the quality of student guidance and student supervision was very good. Supervisors are highly available to help students, and PhD students and postdocs are involved in lower degree student tutoring.

Contacts are maintained mainly with students who defended their PhD, but the follow up of other students trained in the lab is also done. One EPHE student was recently hired as a technician in the unit.

A weekly-based journal club is organized to present new data and methodologies from the literature.

The unit actively participates in student hosting and exchange programs with Ireland, Germany and Italy through Erasmus mundus, and in co-tutoring of PhD students with Tunisia, Algeria and Morocco.

The unit communicates through a prolific output in peer-reviewed scientific journals and the participation of unit members to meetings as speakers. Lab members also gave several interviews in national and regional media (TV and radio).

The unit is involved in international training programs in flow cytometry and in bioinformatics.

Unit members are coordinators of the M2 pro "professional management and innovations in biotechnology".

Short appreciation on this criterion

The quality of student guidance and supervision appears to be good to very good. The permanent staff members are strongly involved in training programs, including their coordination, often as part of their teaching duties as university professors. Recruitment of international students is favoured through participation to international student hosting and exchange programs.

Assessment of the strategy and the five-year plan

The scientific project for the next 5 years focuses on 3 themes: (i) the study of the role of the peroxisome and the pathological consequences of its dysfunction; (ii) the search for lipid biomarkers of X-ALD, multiple sclerosis, and Alzheimer's disease; and (iii) the identification of new therapeutic targets and characterization of new drugs targeting the diseases listed above. As before, the principle axis of research is centered on links between peroxisomal lipid metabolism, oxidative stress and inflammation in the context of neurodegenerative demyelinating peroxisomal disorders. However, new approaches and in vitro tools will be developed (e.g., the creation of an in vitro model of the demyelination process in a context of inflammation). In addition, the ongoing research will be extended to other neurodegenerative diseases in which the role of peroxisomes is suspected. In general, this is a timely and innovative research project that may eventually lead to an improvement of the diagnosis and treatment of patients with (mild) peroxisomal defects (e.g., caused by specific mutations or aging). However, some technical aspects may be challenging and ambitious (e.g., the creation of the in vitro model listed above; understanding the causal relationships between peroxisome (dys)function and redox state in neurodegenerative diseases such as multiple sclerosis and Alzheimer's disease).

The strategy and plan to achieve the ambitious five-year goals are well thought through, and a reconfiguration of the research unit by including 4 neurologists will bring new strengths and opportunities. Indeed, this will (i) improve the critical mass and the quality of research, (ii) stimulate translational research (e.g., through development and improvement of therapies for the diseases under study), (iii) increase the attractiveness of the research unit for talented (medical) PhD students and post-docs (e.g., by strengthening the link between research and clinical practice), and (iv) raise the unit's visibility (the involvement of clinicians will most likely also lead to publications in journals with a higher impact factor). Combined, these benefits will also help to better position the Bio-PeroxIL unit to anticipate funding cuts and reduce the ever-increasing administrative burden, two threats that nowadays often lead to existential problems for many research units.

Short appreciation on this criterion

The unit aims at better defining the physiopathological role of peroxisomes neurodegenerative diseases. The unit will develop original tools that will be useful for the development of translational research programs on validation of biomarkers predictive of peroxisomal defections in neurodegenerative diseases with neurologist who will join the team in the next five year period. Another original promising program will be the identification and characterization of pharmacological targets and modulators of peroxisomal defects. The association of basic scientists with clinicians will strengthened the unit in terms of scientific focusing, scientific production and fund raising. Overall, it is felt that the five-year plan is very good.

Conclusion

- Strengths and opportunities:

This dynamic unit has a very high productivity, despite its small size. The future involvement of clinicians will strengthen the unit by opening new windows of funding opportunities and recruitment of medical students.

- Weaknesses and threats:

The unit suffers from a lack of funding, which limits its scientific progression.

- Recommendations:

The expert committee recommends measures to increase the stability of this group of researchers of remarkable dynamism. We recommend that the unit continues to work on lipid metabolism in peroxisomal disorders, which will improve the scientific identity of the laboratory at the national and international levels, and, to this end highly recommends a strategic analysis on research complementarities and on funding. We strongly recommend that the unit try to better balance the workload between teaching and research.

4 • Conduct of the visit

Visit date

Start: Tuesday 08th December 2015 at 08:30 am

End: Tuesday 08th December 2015 at 04:00 pm

Visit site: Faculté des Sciences Gabriel

Institution: Université de Bourgogne

Address: 6 boulevard Gabriel, 21000 Dijon

Specific premises visited:

Laboratory BioperoxIL

Conduct or programme of the visit:

08h30-9h00 : Huis clos experts

09h00-09h30 : Séance plénière : ouverte aux membres de l'équipe et aux observateurs

Exposé de la politique scientifique de l'équipe :

- activité passée ;
- résultats ;
- stratégie scientifique pour l'avenir ;
- présentation brève et synthétique ;
- accent sur les faits scientifiques marquants;
- évolution significative du positionnement de l'unité (réorientations thématiques);
- administration interne et externe à l'unité.

09h30-10h00 : Questions

10h00-10h15 : Pause café

Huis clos :

10h15-10h40 : Enseignants-chercheurs et chercheurs

10h40-11h15 : Directions des écoles doctorales sur stratégies réciproques de l'UR et les écoles doctorales

11h15-11h40 : Doctorants et post-doctorants

11h40-12h15 : Personnel d'appui à la recherche, administratifs et techniques

12h15-12h45 : Directeur et équipe de direction

12h45-13h45 : Buffet

13h45-15h15 : Huis clos avec les membre du comité d'experts pour établissement du rapport final