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

Section des Unités de recherche

AERES report on the research unit

Chimie des biomolécules, signalisation et processus cancéreux

From the

Université de Limoges

December 2010

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From the

Université de Limoges

Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

December 2010

Research Unit

Title of the unit: Chimie des biomolécules, signalisation et processus cancéreux

Label requested: EA

Former label: EA 4021

Name of the director : Mr Jean Luc DUROUX

Members of the review committee

Committee chairman

Mr Jean CROS, Université Paul Sabatier, Toulouse, France

Other committee members

Mr Pierre FORMSTECHER, Université de Lille I, Lille, France

Ms Françoise NEPVEU, Université Paul Sabatier, Toulouse, France

Ms Dominique WACHSMANN, Université de Strasbourg, Strasbourg, France (CNU représentative)

Observers

AERES scientific advisor

Mr Pierre LEGRAIN

University representatives

Mr Serge VERDEYME, Université de Limoges

Report

1 • Introduction

• Date and execution of the visit

The evaluation took place on December the 2nd , 2010 in Limoges at the Faculty of Pharmacy, part of the University of Limoges. The welcome of the members of the Committee and the organisation of the day were excellent. The visit was made according the following agenda:

- Conversation behind closed doors between members of the Committee to remember the rules of the valuation made by the AERES scientific advisor;
- Presentation of AERES and aims of the evaluation in front of all research unit members;
- Research unit Director presentation (report and project of the research unit)
- Scientific presentation by the three group leaders of the research unit;
- Meeting with each category of personnels (searchers, PhD students, IATOS);
- Interview with the Vice-president of the scientific Committee of the University of Limoges, the Director of IFR-GIEST in presence of the Director of the valorisation ;
- Discussion behind closed doors between the Committee members.

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

The research group entitled " Biomolécules et thérapies anti-tumorales" was created in 2006 and got the label "EA-4021" in 2008. This laboratory was formed by the grouping of several research units of the Faculty of Pharmacy at Limoges. The Univeristy researchers ("enseignants-chercheurs") are biophysicians, chemists and biologists developping research projects in the field of pharmacochemistry of natural products with antitumoral activities.

The research group is localized in the building where all the teaching and research activities of the Faculty of Pharmacy are concentrated. The surface on which the research unit works is important, about 980 m2. The experimental and office rooms are distributed on two levels.

Three main scientific fields are developped by the research unit:

- Theoretical chemistry: molecular modelisation and quantic chemistry;
- Phytochemistry : polyphenolic compounds and redox mechanisms;
- Apoptosis and cellular differenciation: metabolism of arachidonic acid and cellular signalisation.

• Management team

The research group is managed by Jean Luc DUROUX who is also responsible of a research axis and recently elected Dean of the Faculty of Pharmacy.

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	15	21
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2.1	2.1
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	7	
N7: Number of staff members with a HDR or a similar grade	9	14

2 • Overall appreciation on the research unit

- Summary

Several results have been obtained in the laboratory during the last four years in the different areas research.

In theoretical chemistry, the studies mostly relate to the reactivity of specific groups during synthesis using Density Functional Theory (DFT) methods. This is used to rationalize chemical reactions and improve synthesis rates. This was also applied more specifically, coupled to experimental studies on natural molecules such as flavonoids. Together, these studies allow to make some prediction for antioxydant properties of new compounds.

On the apoptosis and differentiation projects, the focus was made on the use of natural compounds, ursolic acid and diosgenin, a triterpene and a plant steroid, respectively, for the induction of apoptosis in cancer cell lines. The results indicate a role of the expression of COX-2 gene for the resistance to apoptosis.

The general assessment of the research unit is very contrasted, with positive points (1) the dynamism, the cohesion and the efforts of the whole staff to go towards a true interdisciplinarity, characterize this unit which is strongly supported by the Regional Authorities; (2) All the University researchers are very strongly implicated in many sectors of teaching and take a good care of their PhDs students. It is to be noticed that this research unit does not host any full time researcher from EPST; and concerns about the scientific strategy (1) the multiplicity of the research topics mainly in biology, does not support the interdisciplinarity posted in spite of the methodological and conceptual expertise of the University researchers and (2) the integration of University researchers, wanted and encouraged by the Presidency of the University is another factor of dispersion.

- Strengths and opportunities

- Association of competences in theoretical chemistry, phytochemistry and cellular biology;

- Sets of themes with the interface chemistry-biology;

- The good state of mind of the various personels : French doctorants and foreigners are proud to belong to this research unit;

- The will to increase the quality of the publications. The impact factor of their publications increased during the precedent four-year plan (close to 3 in 2010);

- A good match for the research actions supported by the Région Limousin.

- A possible opening (even an association) to a laboratory of the University working in the field of the natural substances (EA-1069).

- Recruitment of young University researchers following the retirement of several seniors. The future research topics of these new recruited scientists constitute a challenge.

- Weaknesses and threats

- Dispersion of all topics which alters the coherence of the project in spite of an acceptable assessment on the subjects concerning theoretical chemistry;

- Difficulty to find a scientific positioning; subjects developped in phytochemistry and in cancer biology, in particular, being very competitive;

- No national financial support (failure of two requests to the ANR), and international in spite of the integration of the group "theoretical chemistry" in an European network COST;

- Recommendations

The Committee recommends a significant effort of concentration of the different themes by selecting one or two niches allowing identification natural bioactive molecules that would allow biologists to identify and to use them as tools for studying mechanisms (intracellular and molecular) of cancerogenesis or inflammation. The committee considers as interesting the work in theoretical chemistry but the group must be integrated in the biological set of themes which will be developed. The Committee recommends to strengthen the links with the other laboratories of chemistry (in particular) which develop the same or complementary activities.

It can be understood that university teams are under pressure from their academic authorities to welcome publishing scientists from various horizons, in order to have all publishing scientists and MD's of the university being affiliated to a recognized research team. But, by doing so, they are at risk to be unable to define a clear scientific strategy and to compete properly at the international level. If the goal is to put researchers together to continue publishing at a modest level and to train students and allow them to pass PhDs, this strategy can still work. But, if the goal is to develop an original and promising research on a well chosen scientific niche, to increase the scientific visibility of the university, then the strategy has to be deeply re-envisioned.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	14
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	0
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	14/15
A4: Number of HDR granted during the past 4 years	2
A5: Number of PhD granted during the past 4 years	5

3 • Specific comments

- Appreciation on the results

The members of the Committee noted a different level of information between the document received before the day of audit and the slides presented, those being much more complete.

The fields of the research unit may be summarized as following: (1) Extraction of natural flavonoic compounds, studies of their capacity to scavenge free radicals with experimental and theoritical methods in order to establish correlations to predict their biological properties; (2) Studies of the effects of some polyphenols (diosgenin) on the apoptosis process or on the cellular differenciation mechanisms on some cancer cell models.

However if in each one of these fields some original results were obtained, the general orientation as well as the interdisciplinary of the work does not appear.

Thus the interdisciplinarity put ahead by the members of the research unit did not appear and represented rather a juxtaposition of competences.

The unit produced, between 2006 and 2010, 60 publications with an average impact factor in 2010 of 3.01. This production for 15 University researchers leads to an average of 4 publications (ACL) per University researcher. This is a good performance.

They mentioned two invited conferences, fourteen oral communications and eleven posters. This oral production in national and international congresses is very low. Seven thesis of university were defended (for 14 HDR) and two HDR. The PhD students originate from several foreign countries.

The partnership with the Conseil Régional Limousin is very good. There is no currently valorization of the work with industrial partners.

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

Distinctions or awards have not been reported for the permanent members of the laboratory.

Two conferences were presented.

The diverse origins of the PhD students in term of nationality show the capacity of the Research Unit to accommodate students supported by the Région Limousin. Training of the students in research is made under excellent conditions.

It is surprising that the research unit does not take part in the activity of the Pole de Compétitivité du Grand sud-Ouest (Cancer-Biology-Health).

The budget of the unit relies strongly on regional and local support (42% Conseil Régional; 37% MEN; …). This reflects the good insertion of the laboratory in the regional environment However, the weak budget of the unit limits its influence.

The participation in international programs is limited to an European project COST. Attempts were made at the ANR level without success.

The research unit is well integrated on a regional level: financial support, PhD fellowships.

- Appreciation on the management and life of the research unit

After reading the document, the committee's experts had the impression that no integrated picture of the activities of the different teams was provided. Nevertheless an important effort was made during the oral presentations by the three speakers. Regular seminars are held by the researchers of the different groups.

The fifteen University researchers of the EA-4021 are much involved in the local university formation mainly in the sector “pharmacie”. All of them are over-loaded in hours of teaching and duties that prevent them to concentrate on research as they would like.

- Appreciation on the scientific strategy and the project

Dispersion of the themes decreases the relevance of the project in spite of the will of the various actors. The interface between chemistry-biology is not optimized because of the lack of a common goal.

The Committee strongly encourages the research unit and its actors to work out a new project, in particular within the framework of a process of fusion with the EA-1069 whose activities are closely related to their own. This would allow the unit to reach a size that would permit the development of competitive projects.

The allocated funding and basic supports remain weak and make difficult a policy of attribution of resources and scientific encouragement.

In spite of some original results obtained by each set of themes, the Committee recommends to the unit to set up a project integrating all the scientific actors of the unit which would contribute to a better national visibility and their integration into national and international programs. The quality of young University researchers makes feasible such an approach.

4 • Appreciation project by project

Project 1: Theoretical chemistry and molecular modelisation

- Appreciation on the results

Molecular modeling as a tool to understand and predict chemical and biological properties of natural compounds are carried out in the group of theoretical chemistry which is composed of three University researchers, since several years. The calculation of physic-chemical parameters (descriptors), (e.g., bond dissociation enthalpy, electron transfer capacity, acidity, spin densities) result in excellent correlations between experimental data and calculated values. The demonstration done on free radical scavenging properties of many polyphenols is convincing. These results make it possible to explain the kinetics of transfer of the electrons in the reactions implied between antioxidants and radicals and to predict certain biological properties (antioxidant properties, anti-inflammatory drugs, inhibition of enzymes LOX and COX, anti-proliferative effects). This work led to 7 publications in very good journals of the field and allowed the opening of collaborations with several national teams and European (Tchequie, Spain, Belgium) like with Malaysia. The quality of the results made it possible to the team to be integrated in a co-operation European project in science and Technology (COST 0804 - Chemical biology with natural compounds). This shows the expert testimony of the team in the field of quantum chemistry applied under investigation properties of natural products.

- Appreciation on the scientific strategy and the project

The project of the team is directed towards the study of the trapping of the free radicals formed during the lipidic peroxidation and the capacity of natural antioxidant molecules (polyphenols) to approach the cellular membranes and to be anchored to them. The team proposes to explore molecular architectures polyphenol- cellular membrane by using the processes of molecular simulation of dynamics to study molecular assemblies made up of several thousands of atoms. The project is original and based on a know-how acquired for several years and is complementary to other approaches, carried out in particular within the program COST in which the team knew to be integrated. Thus the team has a scientific niche.

- Conclusion

  - Summary

The team showed its expert testimony in the field of theoretical chemistry and molecular modeling. The process of molecular modeling made it possible to obtain very good correlations between the properties (antioxidant) of polyphenols and the computed values. Although the study of the antioxidant properties of polyphenols were already studied and modelled by various approaches, the processes of calculation implemented by the team are original. The team acquired an European notoriety by integrating a COST program "Chemical biology with natural compounds". The chance to work with a Finnish group having complementary approaches is now given to the team. The Finnish approach (studies of docking between proteins and natural substances) and approaches of the team of Limoges (molecular architectures of natural substances and cellular membranes) must be used as support with the construction of a joint project to obtain financing by the EC.

  - Recommendations

The Committee recommends to the team to strenghen collaborations already established and to integrate international programs in order to raise high scientific level and increase financial supports.

The team showed its capacity to predict the antioxidant properties of natural substances with these modelisation tools and its original approach. The group must now apply them to originale molecules, natural or synthetic, discovered whenever possible by the other teams of the laboratory.

Project 2: Experimental chemistry

- Appreciation on the results

The report mentioned no assessment on the chemistry of synthesis and extractive chemistry. On the other hand the oral presentation showed the good will of the researchers involved in the development of this field. A new young University researcher was recently integrated in this set of themes.

- Appreciation on the scientific strategy and the project

The project presented in chemistry of synthesis in order to obtain molecules with anti-inflammatory drug activity (inhibiting of COX-2/5-LOX) and with antioxidant activities by pharmacomodulation of the flavonoïde skeleton (quercetin) is certainly interesting but public and private international competition is very strong in this field.

The project presented in lichen phytochemistry is very original but the number of scientists assigned to this objective is very limited.

- Conclusion

  - Summary

The pharmacomulation of quercetin and the fractionation of extracts of lichens constitute the principal activities of this group.

  - Strengths and opportunities

Knowledge and expertise in chemistry of synthesis and phytochemistry are appreciated. The integration of a young researcher in phytochemistry is positive. The presence of biologists and chemists in computationnal chemistry is an asset for the discovery of bioactives molecules that indeed requires strategies at the interface chemistry-biology.

– Weaknesses and threats

The human resource on this theme of chemistry of synthesis and phytochemistry is very limited compared to international competition in this field.

– Recommendations

The Committee recommends to this group of chemists to focus, for example, on the original molecules extracted from lichens in order to discover new pharmacophores on which physicochemical modeling could be carried out while connecting them to the biological activities controlled by the group.

The process of collaboration-fusion with the EA 1069 presented at the time of the audit should be made profitable to increase their potential in human resource and scientific effectiveness.

Project 3 : Apoptose et Différenciation

• Appreciation on the results

The activity of the group has been focused on the study of the effects of various natural compounds (ursolic acid and vegetal steroids) on differentiation and apoptosis of several cellular models. Classical methods were used to characterize differentiation and apoptosis and to explore the pathways involved. A specific attention was paid to the connection of these effects with the modulation of expression and activity of Cox-2. The work, rather descriptive, included also mechanistic approaches using pharmacological modulators and siRNA. The most interesting result is the demonstration that Cox-2 is induced by the natural agents used and counteracts their pro-apoptotic effect in cancer cells. The association of coxib's with proapoptotic anticancer drugs could therefore be of interest. However, in vivo confirmation is missing.

Another interesting observation, was that the molecules used were stimulating terminal differentiation at low concentrations and apoptosis at higher concentrations in erythroleukaemia cells, a phenomenon already reported by others with different pro-apoptotic agents inducing terminal differentiation involving death pathways in different cell types, including keratinocytes and erythrocytes. However, the pro-apoptotic concentrations appear quite high (20 microM) and can be a concern for potential medicinal applications, if envisioned. Here again, in vivo confirmation is needed. The ability to trigger differentiation by low doses of pro-apoptotic agents is of fundamental interest and identification of the pathways involved (apoptotic pathway stimulated at low level, other pathways?) is recommended

Members of the team have also a true competence in the field of HHV-6, however this part is not developed in the document and just mentioned in the project.

The group developed good and productive collaboration with another local team of the same federative institute specialized in cell fractionation using the FFF technique (Field Flow Fractionation). However, links of this group with the rest of the team (molecular modeling and medicinal chemistry) appear limited, with no common papers.

From the 60 publications listed for the 2006-2010 period in the report of the team, 43 (72%) are related to biology and clinics. Among them, 26 have a first and/or last author from the team and the rest corresponds to collaborative work done with teams of the federative institute of research in Limoges. The two main topics covered by the original publications of the team are the exploration of the effects of ursolic acid and vegetal steroids on differentiation/apoptosis of various cellular models (10 papers plus 4 in collaboration with a local team) and characterization of HHV-6 virus in human pathologies (8 papers), with a specific focus on Hodgkin lymphoma. Publications appeared in specialized journals with impact factor around 3 and some above 4 (Apoptosis, Int J Cancer, Clin Cancer Res).

The group had a good training activity, with 5 PhD and 2 HDR and 5 PhD in preparation.

- Appreciation on the scientific strategy and the project

The team intends to develop three different projects: (1) A main broad project on apoptosis and differentiation including three sub-projects: (i) in vivo evaluation of the effects of the biomolecules already largely studied in vitro by the team (ursolic acid and diosgenin, (ii) study of the effects of these molecules on hematopoietic stem cells and (iii) study of the role of cyclooxygenase 2 in differentiation and apoptosis of megacaryocytes. (2) A project to explore the pathways responsible for the effects of the product of the DR7 gene of Human Herpes Virus type 6 (HHV-6B) on cell proliferation, and its relation to cancer, in particular Hodgkin lymphoma, (3) A project to explore the effects of tocilizumab, an anti IL6 Receptor antibody, on the production of anti-inflammatory lipidic mediators by human synoviocytes.

These two last new projects are very isolated compared to the principal project on apoptosis and differentiation.

A weak point is the lack of one common scientific question addressed by the team, and not enough scientists dedicated to each project, even if each of them is of scientific interest. With such a strategy, it will be difficult for the team to increase the level of its publications.

- Summary

True expertise of the group. Decent scientific activity, with a modest, but slowly improving mean impact factor of papers. The project is not focused and the strategy should be re-evaluated.

- Strengths and opportunities

The team has a good potential and a real expertise in the exploration of apoptosis and differentiation in several cellular models. The interaction with medicinal chemists is an asset to study the effects and the mechanism of action of original promising molecules.

- Weaknesses and threats

Articulation with the priorities of the medicinal chemistry group is not clear. There are too many and too ambitious projects for a small team.. No focus on one major scientific question. Developping an in vivo model for testing molecules cannot constitute by itself a scientifc objective.

- Recommendations

The committee strongly recommends to select a topic on which the team has a chance to contribute in an original way. To develop a true integrated approach with medicinal chemists. The question of the role of Cox-2 in the control of apoptosis in the context of the use of pro-apoptotic anticancer drugs is extremly interesting, although highly competitive.

An effort should be made to increase the impact of publications. This implies again a more focused approach, deeper mechanistic studies and validation using animal models.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
CHIMIE DES BIOMOLÉCULES, SIGNALISATION ET PROCESSUS CANCÉREUX	B	B	C	C	C

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**

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Université de Limoges

Limoges, le 15 avril 2011

Le Président

à

Monsieur le Président
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OBJET

Rapport d'évaluation S2UR120001482 – EA 4021 -0870669E

Monsieur le Président,

Le personnel et la direction de l'équipe « Chimie des biomolécules, signalisation et processus cancéreux », et l'Université, tiennent à remercier le comité d'évaluation AERES pour la qualité de son travail d'expertise.

L'établissement prend acte du rapport d'expertise de l'équipe, et s'engage à soutenir cette équipe dans sa restructuration engagée l'année dernière, qui va dans le sens des recommandations du comité de visite.

L'autoévaluation menée en 2010 nous a en effet conduits à modifier le périmètre des activités scientifiques de cette équipe, à recomposer ses effectifs, en plein accord avec son directeur et ses personnels. La dynamique engagée alors, les perspectives de rapprochement thématique avec le LCSN dans un calendrier maîtrisé, sont ainsi de nature à permettre au groupe d'atteindre les objectifs fixés dans le rapport d'évaluation. Nous aurions apprécié qu'une évaluation de cette dynamique, dans l'environnement de notre établissement, apparaisse plus clairement dans ce rapport.

L'équipe dirigeante de l'EA4021 souhaite rajouter les commentaires suivants à cette réponse :

Le comité suggère de travailler avec des molécules originales d'origine végétale et de les utiliser comme outils pour étudier des mécanismes de cancérogenèse ou de l'inflammation. L'implication du métabolisme de l'acide arachidonique, notamment la cyclooxygénase-2 (COX-2), dans le contrôle de l'apoptose est une piste à laquelle l'équipe va souscrire. En effet, les biologistes de l'équipe ont une compétence reconnue depuis de nombreuses années sur le rôle de la COX-2 : aujourd'hui, en prenant en compte nos collègues qui ont été intégrés dans le projet de l'équipe, sur les 13 enseignants-chercheurs "biologistes", 7 travaillent sur la relation COX-2 et cancérogenèse, 4 sur la relation COX-2 et inflammation.
L'interface entre la chimie et la biologie se fait déjà aujourd'hui en pharmacochimie par :

- un projet s'appuyant sur une compétence nouvelle et recherchée sur les lichens (du Limousin), avec une recherche de métabolites secondaires qui est et sera bioguidée par les activités biologiques sélectionnées.

- un projet sur une série, obtenue par synthèse, de nouvelles molécules flavonoïdiques non-cytotoxiques capables d'inhiber efficacement l'activité enzymatique de COX et/ou de lipoxygénases (LOX). L'activité de synthèse dans l'équipe évoluera en fonction des résultats du premier projet et/ou des résultats biologiques.

La chimie théorique, compétence reconnue par les experts dans notre équipe, doit effectivement mieux s'intégrer au projet d'équipe dans le prochain contrat quinquennal.

Le processus de collaboration avec l'EA1069 devra se faire pour renforcer notamment notre potentiel en chimie, mais en évitant toute dispersion thématique.

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

J. FONTANILLE