

N2C - Nutrition, croissance et cancer

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Nutrition, Growth and Cancer

From the

University François-Rabelais

INSERM

January 2011



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et de l'enseignement supérieur

Section des Unités de recherche

AERES report on the research unit
Nutrition, Growth and Cancer
From the
University François-Rabelais
INSERM

Le Président de l'AERES

Didier Houssin

Section des unités
de recherche

Le Directeur

Pierre Glorieux

January 2011



Research Unit

Name of the research unit : Nutrition, Growth and Cancer

Requested label : UMR_S INSERM

N° in the case of renewal: 921

Name of the director : M. Stephan CHEVALIER

Members of the review committee

Committee chairman

M. Michel LAGARDE, Université de Lyon, Lyon, France

Other committee members

M. Johannes SWINNEN, University of Leuven, Netherlands

M. Attilio DI PIETRO, Université Lyon 1, Lyon, France

M. Michel RECORD, Université Paul Sabatier, Toulouse, France

Ms. Natalia PREVARSKAYA, Université Lille 1, Lille, France (CNU member)

Ms. Catherine TOMASETTO, Université de Strasbourg, Strasbourg, France (CSS INSERM member)

Observers

AERES scientific advisor

M. Jean ROSENBAUM

University, School and Research Organization representatives

M. Michel ISINGRINI, Université de Tours

M. Raymond BAZIN, INSERM



Report

1 • Introduction

- Date and execution of the visit

The site visit took place on January 13th, 2011, from 9:00 a.m. to 4:00 p.m. After a 30 min introduction by the head of the unit, the four main topics of the research unit have been presented and discussed in terms of project based on the previous results obtained through the last four years. The evaluation Committee then split into three parallel meetings (30 min), with PhD students and Post-docs, technical staff, and research staff. The site visit ended with deliberations of the Committee and writing a draft report.

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

The research project follows a four year period of the INSERM UMR_S 921 entitled "Nutrition, Growth and Cancer", first acknowledged by INSERM in 2002. The former manager was Philippe BOUGNOUX. The unit is located at the University Hospital Bretonneau in Tours, where it uses around 400 m². The research field of the unit deals with the use of specific lipids to control tumor proliferation, metastasis and cachexia. Studies on the mechanism of those lipids include the evaluation of oxidative stress and ion channels.

- Management team

The unit is organized as a single team managed by Stéphan CHEVALIER, University Professor at the Faculty of Pharmaceutical Sciences in Tours.

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	10	13
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)	4	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3.9	4
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	7	12
N7: Number of staff members with a HDR or a similar grade	9	11



2 • Overall appreciation on the research unit

- Summary

The unit has a long standing interest in research at the interface between cancer and nutrition and receives international recognition in this field. The team was the first to link diet-related changes in the lipidome of breast-associated adipose tissue to breast cancer development and metastasis. This finding is of high relevance in view of the mounting evidence that a western diet plays a pivotal role in the development and progression of several common cancer types, including breast cancer. Based on these findings, the team designed a lipid-based treatment that should have great impact on future cancer prevention and chemo-sensitization strategies. Another link between cancer and nutrition has been addressed to cancer-associated under-nutrition (cachexia), a severe clinical condition that often accompanies later stages of cancer progression. Specific dietary lipid intervention may also have important beneficial effects and clinical applications.

- Strengths and opportunities

The main strength of the unit is to make a link between basic research on the possibility of controlling the tumor progression and clinical treatments. This is made possible by strong interactions between university scientists and clinicians within the same laboratory. Being organized with only one team, even developing several topics, also facilitates this translational research. Another advantage is to focus on specific lipids of nutritional value allowing the team to be unique in France.

- Weaknesses and threats

Although some international collaboration is ongoing, this should be further developed to counterbalance the quasi absence of other teams in the field in France. The absence of permanent full-time research scientists may also be a weakness.

- Recommendations

The team should keep going with close collaboration between its members, and continue doing translational research from basic to clinical studies. The variety of research topics needs to be managed sequentially to avoid dispersion.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	13
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 $[(A1 + A2)/(N1 + N2)]$	1
A4: Number of HDR granted during the past 4 years	6
A5: Number of PhD granted during the past 4 years	8



3 • Specific comments

- Appreciation on the results

The research unit has published 84 papers of which 50 with a leading author (1st and/or last) in the list since 2006. Twelve out of the 50 papers have an impact factor over 5. Interestingly to give a trend in the publication policy, 4 papers in press in January 2011 enter in that category (IF >5). More than 60 lectures, with one third in international meetings, have been given upon invitation addressed to one member of the unit. Also, two patents have been deposited in 2007 and 2008, and a third one is in preparation, showing the concern of valuation from the unit. Four different but complementary aspects have been investigated in this one-team research unit, and will be further studied. The main relevant results and projects are summarized below.

One topic deals with the relationship between the fatty acid composition of adipose tissue and the breast cancer risk, as well as the metastasis potential. This is what the team calls a lipidomics signature or the lipidome. This signature, validated in both animal models and humans, can be used as a diagnosis tool that has been patented in 2007. On the other hand, preliminary experiments show that a long-chain omega-3 fatty acid from marine source, namely docosahexaenoic acid (DHA), may potentiate the anti-cancer activity of drugs such as taxanes. The results have been reported in 11 publications, several ones having an impact factor over 5, and several invited lectures in international meetings.

Another and closely related topic regarding the mechanism of breast tumor chemo-sensitization by dietary polyunsaturated fatty acids is investigated. This includes the oxidative stress induced in membranes loaded with DHA and the subsequent toxic effect of reactive oxygen species in cancer cells, and the anti-angiogenic effect of DHA which potentiates that of taxanes. The mechanisms might involve a regulation of the phosphorylation status through the expression of kinases and phosphatases. Those results have been reported in several articles including at least three with an impact factor >5.

A third aspect deals with some ion channels (SK-3 and Nav1.5) that have been involved in tumor progression, i.e. their inhibition by specific lipids reduces tumor progression and invasiveness of breast cancer cells. The expertise of the team in ion channels is quite substantial and several articles have been published, of which two recent ones in *Oncogene* (IF 7.1). A recent application for a patent has been made through "Inserm Transfert", and an initiative to create an open platform of high throughput screening of ion channels has been recently developed for academic and industrial needs.

A fourth topic concerns the cachexia due to denutrition and hypermetabolism, both being associated with cancer. An interesting observation is the increased phosphatidylglycerol (PG) mitochondria from cachectic liver. This is associated with increased oxygen consumption, and a mitochondria dysfunction called hypermetabolism (*J. Hepatol.*, IF 7.8).

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

Several aspects are investigated in the frame of local, national and international collaborations. It must be pointed out that this INSERM unit plays a crucial role in structuring the "Canceropole Grand Ouest" in its approaches in cancer and nutrition.

- Appreciation on the management and life of the research unit

Overall, the integrated investigations summarized above seem to be fully approved by the staff members who adhere to the different proposals.

The unit is quite active in raising funds as the external money has tripled from 2006 to 2010, the current input money being constant during the same period of time. This demonstrates the ability of the team to interact with its socio-economic environment.

Although exclusively composed of teaching scientists and clinicians (no full time research scientist), the unit is deeply involved in research training with around one PhD student per research staff.



- **Appreciation on the scientific strategy and the project**

The research project of the unit extends the four topics that have been summarized above. They appear totally integrated and dedicated to the role of specific lipids in the tumor process and its possible control by nutrition using marine lipids such as DHA or alkyl lipids.

The theme on the lipidome in relation to breast cancer and metastasis will be further investigated with an attempt to non-invasively evaluate the fatty acid composition of adipose tissue by proton NMR (in collaboration with NMR experts on the site). A clinical study on the benefit of DHA in cancer treatment, reported as preliminary, will be extended.

Further investigations on breast tumor chemo-sensitization by dietary polyunsaturated fatty acids are intended to establish the mechanism of action of DHA, in particular through the VEGF action on the kinases cascade and nitric oxide in endothelial cells. Another approach will be the study of PPARs, a field in which the new director of the team has much expertise.

The project of the team on the ion channels will be more elaborated using in vivo models, such as bone metastasis studies, and mechanistic aspects on the mode of action of selected lipids on the function and expression of ion channels will be investigated.

Studies on the under-nutrition topic will now be conducted on the effect of chemically defined phosphatidylglycerol on cachectic mitochondria for oxygen consumption. The involvement of PPAR α , which regulates energy metabolism (especially fatty acid oxidation), will be investigated. Also, an attempt to reverse cachexia with food supplementation by n-3 fatty acids, especially DHA, will be made.

This interesting and ambitious project covers several topics that will be progressively engaged in a process of "go / no go" with possible alternatives.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
NUTRITION, CROISSANCE ET CANCER	A	A	A	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

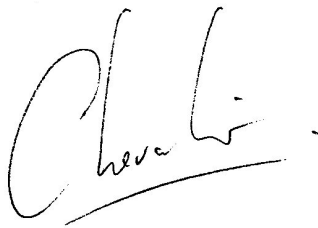
Tours, le 7 avril 2011

SERVICE DE LA RECHERCHE ET
DES ETUDES DOCTORALES

REPONSE DE L'UNITE :
NUTRITION, CROISSANCE ET CANCER
S2UR120001552

"Nous remercions les membres du comité pour l'évaluation de notre unité et la justesse des commentaires apportés sur la cohérence de l'équipe et l'originalité de notre projet situé à l'interface "nutrition et cancer". Nous prenons en compte les recommandations formulées."

S. CHEVALIER



Le Vice-Président,
Chargé de la Recherche



Michel ISINGRINI

