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

Section des Unités de recherche

AERES report on the research unit

Nutrition humaine

From the

Université de Clermont-Ferrand 1

INRA

February 2011

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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 : Unité de Nutrition Humaine

Requested label : UMR_A INRA

N° in the case of renewal : UMR 1019 INRA

Name of the director : Mr. J.M. CHARDIGNY

Members of the review committee

Committee chairman

Mr. Pascal FERRE, University Pierre et Marie Curie, Paris, France

Other committee members

Mr. Jean-Philippe BONJOUR, University Hospital, Geneva, Switzerland

Mr. François BOUCHER, University of Grenoble 1, Grenoble, France (CNU

Mr. Philippe GIRAL, University Pierre et Marie Curie, Paris, France (CNU)

Mr. Hari HUNDAL, Dundee University, Scotland, UK

Mr. Philippe LESNIK, Inserm, Paris, France

Mr. Mario PENDE, Inserm, Paris, France

Mr. Michel RIGOULET, Universté de Bordeaux 2, France

Mr. Michael TISDALE, University of Aston, Birmingham, UK

Observers

AERES scientific advisor

Mr. Jean GIRARD

University, School and Research Organization representatives

Mr. Jean FIORAMONTI, INRA

Mr. Michel BECKERT, INRA

Mr. Philippe DULBECCO, Université d'Auvergne

Report

1 • Introduction

- Date and execution of the visit

The site visit of the evaluation committee lasted two full days, February 8th and 9th 2011. The visit started with a close meeting with the Director, followed by a global meeting with all the people involved in the unit for presentation of the committee and the evaluation process and the presentation of the unit and the main lines of the project by the director. Then the committee listened to presentations from each of the units. The committee had also meetings with staff representatives of the research unit (PhD students/postdocs; engineers, technicians and administrative assistants) and local representatives of the University and INRA. The visit finished with a close meeting of the committee with the director and the committee final meeting. The visit was well organized. All the necessary documents were sent before the visit to the committee allowing to write preliminary reports.

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

The JRU (Joined Research Unit-Unité Mixte de Recherche) is under the dual supervision of INRA and the University of Auvergne. Its configuration results from the merging (on the 01/01/06) of 2 INRA research units located on the INRA site of Theix and the JRU 1019 located on the site of Clermont-Ferrand (Laboratory of Human Nutrition, University Hospital Campus).

In the future project, JRU 1019 will integrate part of the EA 4233 (equipe d'accueil University d'Auvergne) as a team called "Micro Cellular Environment, Immunomodulation and Nutrition – ECRIN".

The overall topic is the role of nutrition in maintaining physiological functions in humans, especially during aging, with studies ranging from cellular models to clinical studies and assessing the physiological needs and the effect of nutrients and nutrition on physiological functions, nutritional status and health. This corresponds to a real socio-economic challenge.

On the 1st June 2010, the JRU therefore has 145 employees, including 101 civil servants (permanent positions). The JRU is organized in several research teams:

- Muscular Metabolic Adaptation (AMM)
- Food, Skeleton and Metabolism (ASM)
- Gene-Nutrients (GN)
- Metabolism, Bioenergetics and Modeling (MBM)
- Lipid Metabolism and Energetics (MLE)
- Micronutrient Metabolism and Health (MiMes)
- Nutrition and Protein Signalling (NSP)
- Proteolysis ()

and common services:

- Experimental Plant for Nutrition (IEN)
- Administrative and Budgetary Management (GAB)
- Metabolism and Mass Spectrometry, which represents the "mass spectrometry" component of a larger structure (Platform for Metabolism Exploration),

The evolution of the JRU for the next 4/5 years will include:

- Merging of the team "Muscular Metabolic Adaptation" with the team "Nutrition and Protein Signalling" to create a new team "Nutrition, Metabolism and Muscular Loss (NMFM)",
- Creation of a new team "Metabolic Phenotype and Preventive Nutrition (MIMEBN)"
- Integration of the EA 4233 as a new team "Cell micro Environment, Immunomodulation and Nutrition – (ECRIN)"

This will increase the number of employees to about 200 persons including 60 scientists, 27 engineers, 30 technicians, assisted by 10 administrative staff persons.

Management has been ensured in 2006-2007 by Mr BOIRIE, along with three assistant directors in 2007: Mr CHARDIGNY, Mr COXAM and Mr DARDEVET.

On January 2008 (beginning of the current four-year contract): M. J.M. CHARDIGNY was appointed director of the JRU, with two assistants: Mr COXAM and Mr BOIRIE. Mr CANO replaced Mr BOIRIE on 1st September 2009.

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

	Past		Future
	UMR 1019	EA 4233	UMR 1019
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	8	17	24
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	37	0	36
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	20	7	
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	57	9	59
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	7	0	
N6: Number of Ph.D. students (Form 2.8 of the application file)	16	8	19
N7: Number of staff members with a HDR or a similar grade	35	11	42

2 • Overall appreciation on the research unit

- Summary

The research in the unit responds adequately to the missions given by the two organizations. The unit, with a critical mass of 9 research teams, covers broad nutritional scientific topics from basic to translational research. There are very efficient collaborations with both health professionals and industrial partners. The Unit has an excellent capacity for fund raising although it could be improved in terms of international funding.

During the last four-year period, its size remained relatively constant, and the quality of published research remained stable. The committee suggests that given the expertise of some groups, the scientific production should increase further in quality during the next four years period in order to remain competitive internationally.

Overall, the JRU 1019 is an experienced research unit very well established regionally with very strong translational approach in human nutrition and a good critical mass, which produces good science, and plays fully its socio-economic role in promoting valorisation and science teaching and training. The Unit manager is a very active and consensual leader and has made a good work during the last four years.

- Strengths and opportunities

This Unit is rather unique in terms of gathering in the different teams such a multidisciplinary experience in the nutritional field with excellent groups in both basic and clinical studies. There is a strong translational research which has proven its efficiency and the Unit is very well established regionally with many active collaborations. The Unit has developed a strong partnership with industry. The Unit thus fulfills the missions given by INRA.There are also excellent technical platforms (metabolomics, animals), and a privileged access to the Nutrition Center for investigations in humans (CRNH). Finally there is a very active management.

- Weaknesses and threats

The teams are heterogeneous in terms of scientific production (with some excellent groups and some weak ones), attractiveness and quality of the project. Often, the projects are not enough structured and globally too dispersed with some expertise lacking for their achievement. Two fields of expertise should be strengthened : cellular and molecular studies and bioinformatics. Such an improvement could be achieved by attracting young researchers and groups in the new unit. Similarly the experience of governance and scientific influence of the various team leaders is uneven. Active collaborations between the teams must be improved all the more as some of the projects appear quite similar or complementary. This could be achieved through better communication inside the Unit. The spliting of the teams into two localizations could be an obstacle to the development of these interactions. Interactions between basic and clinical research remains to be strengthened in some teams.

- Recommendations

Beyond the traditional skills of the unit in nutrition and biochemistry, it is necessary to improve skills in bioinformatics and integrative physiology (mechanistic models). The unit should be strengthened through the recruitment of young (post-doctoral) researchers able to develop cellular and molecular models of clinical relevance in order to promote interactions between basic and clinical research. An increase in the number of clinical faculty researchers should boost clinical research. Most of the teams should restrain the number of their projects in order to develop a more vertical and in-depth research. It is strongly recommended for the team leaders to be ambitious for their publications since the Unit will evolve in a more and more competitive environment. Concerning the metabolomic projects, it is necessary to have a global approach and not such a dispersion among several teams.

It is also probably necessary to rediscuss the future of the weakest teams. Merging with more solid groups is a possibility. The managing committee should try to improve the flow of informations between teams through regular formal and informal meetings and must be vigilant concerning the remoteness of the two geographical sites.

- Production results

	Future
A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	24
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	35
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	98%
A4: Number of HDR granted during the past 4 years (Form 2.10 of the application file)	3
A5: Number of PhD granted during the past 4 years (Form 2.9 of the application file)	6

3 • Specific comments

- Appreciation on the results

Quantitatively, the research unit produced during the last four years about 100 publications/year including 15% with impact factor > 5. For the whole unit, there are 2 publications in journals with an impact factor >10 for the last 4 years. Qualitative analysis shows that the quality of papers remained stable. One obvious limitation is the moderately high impact factor of the journals in the field of nutrition. Nevertheless, the committee felt that some group leaders could be more ambitious in their publication strategy.

The JRU 1019 contributes to research training, with 16 PhD students in the lab in 2010 and 27 having obtained their PhD thesis in the last four-year period. Nine researchers obtained their HDR during the reporting period. Overall, the activity of the JRU 1019 has provided a solid contribution in terms of teaching to the Clermont university. It is strongly involved in “nutrition and food sciences” masters.

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

The JRU 1019 has a very good national visibility. This is attested by its efficiency in raising funds from ANR, AFM and PHRC. From an international perspective, some teams have ongoing international collaborations, but there is a weak involvement in European programs. There is a dense and strong collaboration with industrial partners. But this collaboration based on limited projects is probably also an impediment to development more in depth research (mechanistic models). Between one third and one fourth of the research budgets comes from private research contracts. International projects provide between 10 and 15% of credits and national projects (ANR, PHRC) around 50%.

The recruitment of students and post-docs is essentially local. The relatively limited international visibility of several teams may also explain the modest number of international post-docs in the unit, and the absence of newly recruited teams that do not come from the local research tissue. A difficulty for attracting international post-docs may be the language barrier. More efforts should be made to have seminars and lab meetings in English, in order to provide a more welcoming atmosphere for international visitors.

It seems necessary to increase the number of seminars for students and improve services to the site of Theix (last shuttle for down town at 5 pm !!) .

The general organization of the research unit is based on fully independent research teams, basic common facilities and administrative services. This organization seems generally appropriate in regard to the needs, although the absence of a rewarding system (e.g. specific fund allocation, technicians) for the best teams does not stimulate competition between the teams.

The discussion with the laboratory representatives did not show any particular problem, but there is some heterogeneity between the teams. It would be desirable to specify a more general policy for the signature of engineers and technicians in publications. There is also a demand of ITA to be more involved in the development of projects.

- Appreciation on the scientific strategy and the project

The project is in continuity with what was done previously. The quality of the presentations was very uneven among the various teams. The teams which are the most successful are those who are doing mechanistic research and they will continue to develop their projects along these lines. In contrast, teams involved in translational/clinical research, must focus their research on a small number of realistic topics (see team reports). This will allow to still improve the publication record.

Several teams have projects of metabolomics, which is legitimate if one considers the history of this unit and the INRA specific demand. However, there is a contrast between a major technological platform (10 mass spectrometers) and dispersion of projects between teams and the absence of a real bioinformatic taskforce to cope with all the generated data. It is necessary to be realistic and to ask researchers to develop a global project because it requires very substantial forces both in terms of material and human resources. This should not prevent the search "à façon" with industrial partners which has reveal very successful and also correspond to the Unit missions.

Following the recommendation of the committee in 2006, teams have been merged. In the new project, new teams are proposed but paradoxically, they are not always the strongest ones.

The capacity of teams to respond to invitations to national programs (ANR, PHRC) and to obtain external funding (regional or industrial contracts) is very good and should allow the unit to secure over 70% of its budget in this way.

Finally, beyond the heterogeneity of teams and research topics that reflect the diverse aspects of nutrition, the unit has a strong research structure with local roots and a very important expertise nationally and internationally recognized; this should enable to carry the bulk of the project after choosing the most promising and realistic topics.

4 • Appreciation team by team

Team 1 : Proteolysis

Leader : Mr. Didier ATTAIX

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	5	5
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	0	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	3
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 2.8 of the application file)	2	
N7: Number of staff members with a HDR or a similar grade	4	4

- Appreciation on the results

Proteolysis of skeletal muscle is common in a number of conditions and current therapy is limited. It is therefore important to understand the mechanism by which this occurs, and to use this information to develop new therapeutic agents for treatment of this condition. This is the aim of this research group which is producing highly original results, highly relevant to this objective. Their fundamental studies have led to the interesting hypothesis that manipulating proteolysis in the small intestine would also increase muscle protein mass. Using GLP-2, a gut trophic factor they have shown an increase in muscle mass in starved and re-fed rats, and plan to use GLP-2 as a therapeutic agent to limit muscle atrophy and accelerate muscle recovery in catabolic states. This finding, however, would have been strengthened if they had used a second model of muscle wasting, such as cancer cachexia, since dietary restriction may impair the ability of the intestine to take up nutrients on re-feeding in a different way from other catabolic conditions. This work has not been published yet, possibly because of patent considerations. An important area of research undertaken by the team is to identify proteins in muscle, which are degraded by the proteasome. This work has been published in some high impact journals, and the team are world leaders in this area of research. Using a new technique that they have set up, the team has identified for the first time that several myofibrillar proteins including myosin heavy chain, telethonin and actin are proteasome substrates. Another important observation by the team is that both the ubiquitin-dependent proteolytic system and the mitochondrial-associated apoptotic pathway are activated during muscle atrophy, while in the recovery period the proteasome pathway is normalized rapidly, while there is a late normalization of the apoptotic process, suggesting a biphasic recovery phase regulated by different effectors.
Other studies have identified changes in skeletal muscle with ageing, using the rat as a model. Analysis of the proteome of such animals have revealed 58 different markers of sarcopenia, and it would be interesting to see if similar changes occur in human muscle from aged subjects.

The group has published 18 refereed original publications and 5 review articles since 2006. While the number of publications is not high for a group of this size they have achieved publication in some high impact journals of the field (J. Physiol, J. Biol. Chem. Nutrition, J. Nutr Biochem., Rheumatology), which has given them international recognition (they have been invited to write a preview in Cell Metabolism).

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

This has led to invitations to 3 scientists of the team to 12 international congresses and to 8 seminars or conferences, and the group has a high international profile. In addition the team leader is on the Editorial Board of three leading international journals in this area, as well as being a member of numerous, mainly national committees. As expected of a team with international recognition the group members are invited to review numerous scientific publications in leading international journals, as well as grant applications both nationally and internationally. They also have served as external reviewers / members of the jury of about 10 PhDs and HDRs, as well as being involved in the recruitment of associate scientists and professors at the INRA and at Clermont University. They also serve as consultants for two leading international pharmaceutical companies. The team has been very successful in attracting continuous research funding over the period, both from national and European sources (3 ANR with 2 coordination, participation to an EU grant, 4 AFM and 1 InCa grants). The group also has partnerships with three industrial companies, which also has grant support. The group has extensive outside collaborations, both with national organizations (8) and international (7). This has led to numerous joint publications. Internal collaboration with two groups of the JRU has led to 10 joint publications. The team leader has also been involved in the organisation of two congresses in Clermont-Ferrand, on one of which was international. The work on GLP-2 has also led to a European patent application, which is essential if clinical development is to progress.

The team leader is strongly involved in university education at Clermont University, being Director of the Master for Nutrition and Food Sciences. This provides a good opportunity to recruit PhD students, and scientists for INRA. He is also involved with the International Training Centre's Degree in Human Nutrition and Food Sciences, and is a member of the Educational Council of the ED65. The group therefore has high quality links with international, national and local partners. The group has no post-doctoral scientists and no scientist is from abroad.

- Appreciation on the scientific strategy and the project

The size of the team is appropriate for the research activities proposed, particularly since there is extensive collaboration within the unit. There may be scope for further collaboration with the "Nutrition, Metabolism and Muscle loss" team since there is a degree of overlap in the work of these two groups. They have developed a sound scientific strategy to investigate the problem and are using state of the art modern approaches and appropriate biological models. The team proposes four scientific projects, which continue and expand their previous studies. The work proposed is relevant to their overall aims, and ranges between in vitro and in vivo studies in animals to a clinical trial of GLP-2 in patients with chronic renal failure undergoing hemodialysis and exhibiting muscle wasting. Most of the techniques that are to be employed in the projects are established, either through previous work by the team, or are published in the scientific literature. Thus the projects are feasible, and should be achievable during the 4 year period. The work is original and covers areas that have not been previously investigated, e.g. the role of intestinal microbiota on muscle mass, and characterization of predictive markers of sarcopenia in humans, which follows on from their previous studies in rats. The E3 ubiquitin ligases recognize protein substrates for degradation by the proteasome, and are potential targets for therapeutic intervention to reduce muscle proteolysis in catabolic states, and one of the projects investigates which E3 ligases are responsible for the breakdown of contractile proteins using an innovative technique (Surface Plasmon Resonance, coupled or not with mass spectrometry). However, the E3's also play an important role in regulation of muscle mass under non-pathological conditions, and interference with their function could result in abnormal muscle mass, or function. The science of the E3/substrate interaction, and the specific E2 enzymes acting in concert is cutting edge, and will be conducted in collaboration with Dr Stewart Lecker at Harvard Medical School who is part of one of the major international groups investigating this process. Other projects, e.g. characterization of established or predictive markers of sarcopenia in humans also use the cutting-edge techniques of transcriptomics and proteomics.

In summary all projects are highly original and are technically feasible.

- Conclusion :

  - Summary

This team has a strong and broad expertise in the field of skeletal muscle protein degradation. The field of study is 'cutting-edge' and appropriate for the development of therapeutics designed to prevent or limit muscle wasting in pathological conditions. The appropriateness of the research path is evidenced by the success of the team in attracting research funding, both from governmental and industrial sources. Most of the research is of high quality and is published in high impact (IF 4 or above) international journals. The team has a high international profile as evidenced by numerous invitations to speak at scientific congresses, editorships of international journals and requests for grant and scientific paper review. The projects for the next four-year period are clearly focused and appropriate, and continue on the success of the previous four-year period. The group collaborates extensively, both with JRU 1019 and outside, both nationally, and internationally. Any further expansion of the group through post-graduate or post-doctoral workers could come through external funding, which would raise the overall revenue from this source. Currently the income on each grant is relatively modest, probably because they only fund consumable costs.

  - Strengths and opportunities

There is an International recognition of the work and the research is cutting edge, with publications in recognized international journals. The team is attractive to outside research fundings and the projects are clearly focused. The team leader is strongly involved in university education which should allow to recruit high quality students.

  - Weaknesses and threats

There is a high outside competition with E3 substrates and the group should increase its efficiency through the recruitment of post-doctoral fellows.

  - Recommendations

It is necessary to recruit post-graduate or post-doctoral workers. This should increase the efficiency in terms of publication. Considering the field and the results obtained up to now, the team should consider to publish in highly rated journals.

Team 2: NUTRITION, METABOLISM, MUSCLE LOSS

Leader: Mr. Yves BOIRIE

- Staff members

	Past NSP	Past AMM	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	6	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	6	2	4
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	2	3	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	6	2	7
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	0	
N6: Number of Ph.D. students (Form 2.8 of the application file)	2	2	
N7: Number of staff members with a HDR or a similar grade	4	5	8

- Appreciation on the results

This team will result of the merging of two groups whose common interests are the metabolic adaptations of skeletal muscles during pathophysiological conditions. The team masters a number of in vivo techniques to assess physiological parameters in humans and animal models. It is widely recognized at the international level in this domain of research, as attested by the high number of publications and invitation to scientific meetings. In the last 4 years the team has addressed the following issues and their impact on muscle function: effect of protein intake, amino acid composition and kinetics of protein digestion; sarcopenia during ageing; detrimental effects of inflammation, obesity and lipid deposition; possible therapeutic interventions such as caloric restriction, supplementation with antioxidants, sulfur amino acids.

This research led to a very high number of publications in peer-reviewed journals (140). The majority of the work has been published in the best journal of the field (Journal of Physiology, American Journal of Clinical Nutrition, AJP, FASEB J). The average impact factor of the 10 best publications is 5.981, reflecting publications in the best journals specialized in the field of muscle physiology and human nutrition.

The team has numerous and strong partnerships with hospital and pharmaceutical/nutritional industries. Collaboration with basic scientists addressing molecular mechanisms of the described physiological responses is lacking.

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

The team is composed by a high number of tenured scientists who are regularly invited to national and international meetings (47 for the later) in the field of muscle physiology and nutrition. An important number of grants from ANR (7) and industries have been recently secured. The team members are principal investogators in 4 PHRC. There is one participation in an EU contract. Two patents are mentioned. The Pi is president of the scientific council of a european society (European Society for clinical nutrition and metabolism) and has organized a meting in this context. He is also a member of the French Agency for food safety and of High Health authority.

The number of qualified French and foreign post-doctoral fellows is rather limited.

- Appreciation on the scientific strategy and the project

The future projects are in line with ongoing research. They are highly feasible, considering the wide expertise of this group in the field of human nutrition and muscle physiology. Given the high number of permanent positions in the team as well as the important budget that has been secured, it would be wise to consider 1-2 cutting-edge projects, developing new experimental approaches and scientific questions and including in depth mechanistic studies. The project on vitamin D action seems to go in this direction, integrating human physiology, animal models, molecular studies, clinical trials and functional approaches.

- Conclusion :

  - Summary

This is a large team with a strong background in muscle physiology, nutrition and protein synthesis, well recognized on an international level. The team has developed many clinical studies in important fields such as sarcopenia. They have a long publication list with an appreciable number of papers in the best specialized journals. They have secured a large amount of funding (although international funding is not well developed) as well as numerous collaborations including with industrial partners.

  - Strengths and opportunities

Undoubtly their connections with hospital and nutritional industries is a strong point, allowing to develop clinical studies in humans. They are addressing important topics related to socio economic questions such as muscle loss and dependency during aging. They master a number of original techniques allowing in vivo measurements of muscle function and protein turn-over. Their know-how and the large size of the team should allow to develop cutting-edge projects.

  - Weaknesses and threats

Functional studies and investigations of novel molecular mechanisms are still rather limited. These approaches should be developed, in order to address the scientific questions in depth and to publish in high ranked general journals.

  - Recommendations

The team should establish the experimental tools and collaborations in order to provide mechanistic insights that may explain the observations on human physiology. It could be helpful in this context to hire qualified postdocs bringing new expertise in functional and molecular studies and allowing to develop relevant animal models. This should allow to publish in excellent journals such as the J. Clin Invest. for instance.

Team 3: Integrated metabolism, metabolomes and nutritional biomarkers

Leader: Mrs. Blandine COMTE

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		2
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
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)		
N7: Number of staff members with a HDR or a similar grade		2

- Appreciation on the results

This team emerges as a new one and there is no common past for its members. The team leader was previously in another team of the JRU where he worked on oxidative stress. During the reporting period the number of publications is low (5) with only one paper as last author in a journal with a modest impact factor (Journal of Cystic fibrosis, 1.5).

The quality and impact of the results are thus weak. The second member of the team is a young researcher and he was previously in another INRA center, working on fish metabolism. His publication record is very good, 29 papers, most of them as first author and in good specialized journals (e.g. Am. J. Physiol). Despite this good record, It must be underlined that he has no experience in "omics" (see below).

In summary, the scientific output in the future topic of the team is low.

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

There is no mentioned invitations to international congresses.

The Pi has still collaborations with the group in which she was working previously in Montreal before joining the JRU 1019. The team is linked with several local teams and national teams as SUVIMAX for bioressources collections. The team aims at recruiting one Associate Professor for bioinformatic analysis of metabolic patterns.

Two PhD students are working on the team project but apparently no PhD thesis was supervised during the reporting period. No post-doc is mentioned.

The team participated to the 6th FPU European projects (EURECCA and NUGO), but no publication is found related to the activity of the PI. The PI coordinates an ANR grant (ANR-DFG) and has industrial partnerships. The team leader has one patent (2007).

Considering the various indexes described here, the attractivity of the team is modest.

- Appreciation on the scientific strategy and the project

One of the original aspects developed by this small research team is the application of "omic" approaches particularly metabolomics to address two main questions

1) identifying early metabolic events associated with "nutritional transition", a phenomenon well known to be associated with variety of chronic diseases including metabolic diseases and,

2) identifying biomarkers of food intake (and or food typologies) which can be modulated by different factors in human beings.

The project is highly dependent on bioressources especially in getting body fluids and tissues from well phenotyped populations (collection performed by other collaborative teams) and on a technological platform (Mass spectrometry), to identify relevant metabolites in the two axes. Of note, analyzing the data at large scale is a real challenge necessitating the combination of bioinformatics and biostatistics. This approach is an hypothesis generating approach and can be considered at "at risk approach" but which could be essential in the future to identify fingerprints of food consumption and early markers of diseases.
Three main projects are presented

Project 1: Metabolic and oxidative modulation.

The metabolic approach is conducted in a large variety of models ; animal models (nutritional, genetic, rats, swine), and human preclinical models, from several fluids including plasma, gut microbiota in animal models and in response to a variety of challenges (for example inducing changes in the redox and inflammatory state). The different animal models are not described with great precision. These projects are supported by several ongoing projects (BIeNNat, EURRECA) and the PI received recently an ANR-DFG grant (2011-2013).

Project 2: Metabolic orientation and nutritional transition

This project is closely linked to the activity and model development of another team "Nutrition, Metabolism and Muscle Loss" in the Met Across project. It aims at evaluating the nutrients profiles in pig submitted to nutritional changes in order to induce insulin resistance. Different tissues and fluids are studied in the same animal. This project is a strong technological challenge in particular in the use and development of (new) bioinformatic tools, for data integration, treatment, analysis and visualization to evaluate metabolic fluxes. The project is highly dependent on the pig model study performed by the team "Nutrition, Metabolism and Muscle Loss". A support from other teams with stronger bioinformatic support is clearly needed. Knowledge might be nevertheless produced to the research community

Project 3. Food metabolome

The main objective here is to characterize biomarkers (metabolite) of food intake. The team has for example identified metabolites associated with the consumption of citrus in individuals from the SUVIMAX cohort. This can be applied to body fluid collected from well phenotyped population in which food intake characteristics are precisely collected. Large scale is necessary considering the high individual variability. In addition the project mentions the utilization of genetic markers to be combined with metabolites. The power of such study is a crucial issue and the capacity to study fluids at large scale is not presently obvious.

Nevertheless, finding fingerprints of food intake consumption could have an impact on nutrition epidemiology and food industry in the future.

- Conclusion :

  - Summary

This new team is led by a researcher with a weak scientific impact and both researchers have a modest experience in the project field. The project is extremely ambitious with a huge numer of models and experimental conditions (including human gene polymorphisms), and a large dependency to well-phenotyped human cohorts and animal models of other teams of the UMR and outside groups. In addition, the "omics" and integrated approach requires competence that are not presently found in the team and requires a large number of people working on the bioinformatic side (at present only an MCU, not yet recruited would represent the main task force in bioinformatics and data mining). This program should also reveal extremely expensive.

  - Strengths and opportunities

The project is original particularly the food metabolome which aims at identifying biomarkers of food intake (and/or food typologies). It could be an opportunity for the UMR and INRA to take the lead on this topic.

  - Weaknesses and threats

The team leader has not yet demonstrated its capacity to lead such a project. The project is far too ambitious for such a small team and it must focus on one or two protocols at most, allowing to demonstrate its know-how. The absence of a strong bioinformatic experience is a major threat for this project The project also highly relies on external ressources (human cohorts, animal models).

  - Recommendations

If this field represents a major challenge for the UMR and for INRA, then the team must be reshuffled in such a way that it becomes credible. Strong expertise in "omics" as well as a true bioinformatic group must be provided (the later could become an independent entity in the UMR providing its experience to all teams when necessary). The committee was unanimous to think that the present team is not in adequation with the project.

Team 4: Food, Skeleton and Metabolism

Leader: Mrs. Véronique COXAM

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	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)	0	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4	4
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)	2	
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

The scientific production of the ASM team essentially pertains to the prevention of human osteoporosis with the long term aim of providing evidence for beneficial effects of selected nutrients on bone health. Over the past 5 years the scientific production is substantial, with 38 original articles most related to bone metabolism studies. Among them 16 have been published in journals with impact factors ranging between 2.7 and 6.7. These papers deal with the effects of nutrients on bone metabolism studied in animal models, mainly rats, and a few concern trials in postmenopausal women. The most original findings are related to the in vivo and in vitro effects of some polyphenols such as the citrus fruit hesperetin and its circulating metabolite, hesperetin ñ7-O-glucuronide (Hp7G). Investigations on the effect of prebiotic compounds or alcalin salts appear to be less promising. Animal models of osteoporosis is the best technical skill and long term experience of the team. So far their expertise is somewhat less in cellular and molecular bone biology. The significant scientific activity level is also reflected in several book reviews (n=10).

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

The ASM impact is quite noticeable, as reflected by active participation to various expertises at both international (e.g. ILSI-Europe, DFG) and national (e.g. AFSSA, INCA, ANR, AERES) levels, Editorial Boards (e.g. British Journal of Nutrition), congress organization, and grant awards from European (EU thematic network, European Spatial Agency) and French institutions (1 ANR as a collaborative team, INRA grants) and 4 industrial grants including a CIFRE thesis. The large number of scientific collaborations with both academic and industrial partners, in France and abroad, can also be considered as a positive accomplishment. Moreover, the attractiveness of the ASM laboratory can be valued by the participation of foreign researchers (Leonardo program) to the research activity. Team members have been invited to a large number of congresss (n=37) at national (21) and international (16) events, and have supervised three PhD thesis.

- Appreciation on the scientific strategy and the project

The general aim is to pursue the research lines followed during the past 4 years, with some substantial modifications. Particularly, the "acidosis" topic will be given up, which appears to be a rather reasonable option, taken into account the negative results of their 2008 related study. Among new directions, the impact of nutritional compounds on aging processes will consider not only that the effects on bone metabolism and osteoporosis, but also their influence on other organs/systems, more specifically: skeletal muscle and adipose tissue. Emphasis will be given to the potential effects of micronutrients other than calcium and lipids.

Specific projets

1) Contribution of fatty acid to physiopathology of bone remodeling.

The project is too succinctly described. The state of the art delineating current knowledge is not presented. Methodological approaches are not detailed. Therefore, although the project seems interesting, its value in terms of originality, potential impact, feasibility, and chance of success cannot actually be estimated.

2) Functional role of micronutrients to limit the process of osteopenia.

Mechanistic studies aimed at delineating how selected micronutrients can exert effects that pertain to their positive anti-oxidant and-or anti-inflammatory effects on bone remodeling are worth to be undertaken. It is not clear which preclinical evidence will be requested for designing and launching intervention studies in either postmenopausal women or elderly subjects, knowing how much clinical trials are humanly and financially demanding.

3) Integrated approach to nutritional prevention of osteoporosis.

This is quite an ambitious program with various aims and involvement of many actors from the academic and industrial world. The three parts of the program are heterogeneous, uneven in their description and respective objectives.

- Conclusion :

  - Summary

During the past four years, the scientific production has been quite substantial with some original articles published in journals, with modest to good impact factors in the nutrition science category. Other bibliographic contributions, invited lectures, congress communications and participation to scientific evaluations testify the dynamic activity of the ASM team. Taking into account this noticeable accomplishment during the past activity period, the presentation of the projects is not as rigorously developed and structured as one would expect from such an important research application covering a five year ambitious program.

  - Strengths and opportunities

The acquired experience in animal models of human osteoporosis and the expert management of nutritional interventions in these animals is clearly a strength. The nearby outstanding scientific teams of the UMR 1019 Unit, implicated in nutritional research at the molecular and cellular levels are also opportunities if active collaborations are established. The project is supported by efficient laboratory and equipment facilities for animal research.

  - Weaknesses and threats

One of the main weaknesses is the locally relative lack of both past experience and availability of the medical staff for osteoporosis clinical research in order to translate promising preclinical studies into well designed and powered human investigations. One must also emphasize the limited number of mechanistic projects at the cellular and molecular levels which could limit the impact of publications. Finally, there is a real risk of rapid takeover from nutritional and-or pharmaceutical firms of any bone bioactive molecules of interest, isolated and first tested by the ASM laboratory.

  - Recommendations

It will be necessary to secure clinical studies by including a medical specialist of osteoporosis. The team must develop more mechanistic studies possibly through local collaborations. It might be safe to restrict the number of projects in order to allow more vertical studies leading to high impact publications and to have a clear and detailed view of what will be performed.

Team 5: Genes Nutrients

Leader: Mr. Pierre FAFOURNOUX

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	5	5
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	0	1
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)	0	
N7: Number of staff members with a HDR or a similar grade	2	2

- Appréciation sur la qualité scientifique et la production Appreciation on the results

The research focus of this team over the past quadrennial period has been to develop three distinct, but related themes addressing the impact of amino acids on (i) gene expression and cell signaling in mammals, (ii) regulation of physiological functions and (iii) complex pathologies that may or may not have a nutritional basis.

Despite the unavoidable disruption in the work programme due to maternity leave by two of the full time researchers, the team has made good progress in developing the three thematic areas as judged on the basis of measurable outputs. The work has led to publication of 17 articles/book chapters, of which 14 are in peer reviewed journals. Of these 14 papers, 5 have been published in journals with an impact factor of greater than 5.0. Whilst the merits of journal impact factors is a much debated and contested issue those with impact factors > 5.0 are highly regarded in communicating research that is considered both novel and significant. In any event, the team has been consistent in publishing their findings in high quality mainstream biomedical journals and consequently has been successful in disseminating their work to a broad scientific audience.

The research that has been performed to date is both novel and relevant to improving our understanding of the impact that availability of simple nutrients (i.e. amino acids) have upon the physiology and pathology of cell and tissue function. In particular, the recent in vivo validation of the importance of the GCN2/eiF2alpha/ATF4 pathway with regard to regulation of TRB3 expression (published in PLoS ONE) and the identification of the upstream signaling events that enhance ATF2 phosphorylation in response to amino acid lack represent important advances in the field.

The team has also made some interesting observations with respect to the role of GCN2 in the central control of food intake. This represents an important area for future development.

Other ongoing works include the molecular events that may influence nutritional imprinting of genes in response to poor protein nutrition in utero and the adaptation of cancer cells to amino acid starvation

The research team appears cohesive based on shared authorship of research articles and the grouping has a number of established collaborative links both nationally and internationally. These collaborations have facilitated some of the current outputs from the team and seem critical for some of the ongoing studies and those planned for the future.

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

As evinced by (i) the published studies on regulation on amino acid regulated genes carried out in collaboration with colleagues in Florida, (ii) the ongoing studies investigating the role of the Anterior Piriform Cortex and hypothalamic GCN2 on regulation of food intake being performed in collaboration with researchers in Paris and Dijon and (iii) the work on cancer cells with collaborators in Nice the team is proactive in forging effective research collaborations at both national and international levels.

Despite the significant output and impact of the work generated by the Gene Nutrient group it is some what surprising that only the team principal has thus far had invitations to international (3) and national (5) meetings, which suggests that greater networking and exposure of other members of the team is needed in order to raise the groups profile (i.e. beyond that of the team leader alone) on both the national and international stage. It is highly likely that by doing so that the group's collective ability to recruit new investigators, post-docs and students, especially from abroad, would be enhanced as would their capability to compete and attract much needed external funding.

- Appreciation on the scientific strategy and the project

During the evaluation visit the team leader presented a coherent account of the groups past and proposed work. The team's future research strategy aims to proceed on three parallel fronts that utilize a multi-disciplinary approach to (i) identify the membrane bound receptor that interacts with G 12 to promote activation of JNK and ATF2 phosphorylation, (ii) further studies aimed at validating and visualizing the functional operation of the eIF2alpha/ATF4 pathway in vivo and (iii) defining the signaling pathways regulated by amino acid availability that underpin changes in growth and metabolism that arise as a consequence of nutritional imprinting and cellular adaptation to altered nutrient availability.

The proposed programme of work is original and builds intuitively on studies conducted during the past four years and remains relevant to the remit of the Gene Nutrient team. Specifically, the development of a mouse model expressing the AARE-LUC transgene offers considerable potential for monitoring the control of nutritional signaling via the eIF2alpha/ATF4 pathway both in response to GCN2 activation and non-GCN2 pathways if these mice were to be crossed with GCN2-/- mice. Considerable focus is being placed on delineating whether GCN2 activation in POMC and/or NPY neurons may play a role in food aversion in response to a leucine-free diet and whether GABAB receptors form part of the neuronal circuitry regulating the GCN2/ATF4 axis. These studies along with those investigating the acquisition of imprinting marks from mother to foetus, whilst clearly innovative, are technically challenging and critically dependent upon maintaining stable collaborative partnerships to ensure that the work develops at an appropriate pace over the coming 4 years.

A budget management programme for UMR 1019 is clearly in place and there appears to be a functional mechanism that governs allocation of resources within this Unit. However, it is unclear from the information provided whether the resource allocated to the Gene Nutrient team over the current quadrennial review period has been sufficient in realizing the original goals/objectives or indeed whether the allocation model will adequately support the future work being proposed.

- Conclusion :

  - Summary

This is a cohesive research team, which despite having lost one member of their group to another JRU team has recently been strengthened by the recruitment of two junior research (CR2) staff. The team has been productive as judged by analysis of publications in peer-reviewed journals, invitations to national and international meetings and presentation of data via oral and poster communications at numerous congress meetings. Some of the published findings have been very novel and this has helped to maintain the team's international standing in the area of amino acid regulated gene expression. It is also evident from the the exciting programme of work that is being proposed that the group will remain at the vanguard of new developments in this reasearch field.

  - Strengths and opportunities

Given the long standing interest that the Gene Nutrient team has in trying to undertstand the molecular mechanisms that contribute to amino acid sensing/signalling they are clearly in a position of strength, in terms of track record and experience, in continuing to not only make an impact in this field but to shape the future direction of this important area of biomedical research. The team shows considerable versatility in its activity as demonstrated by their ability to integrate mechanistic studies carried out at the cell and molecular level with work in whole animals. The proposed programme of work is both novel and progressive and shows considerable originality in design and potential impact.

  - Weaknesses and threats

Although the overall productivity of the group has been good it is clearly being compromised by the fact that the team has a poor level of post-graduate supervision and very few post doctoral staff. Without such indiviuals the team run a serious risk of not being able to maintain a competitive presence in what has become a fast moving research area. The team needs to minimise this risk by not only strengthening, but enhancing the network of collaborations and to submit more applications for external funding to not only help support the recruitment of talented post doctoral staff, but to also try and mitigate some of the running costs associated with the projects being proposed.

  - Recommendations

There is considerable local expertise within JRU 1019 on topics that are revelant to the Gene and Nutrient research programme (e.g. the MBM, EA4233, MIMEBN and NMFM groupings). Whilst it might be implicit that the groups operate in a collegiate and collaborative environment it was not clear from the documentation whether the resident expertise is being exploited effectively. The team should identify common interests with other JRU groups and make use of any resident expertise and technology that would help advance their own research objectives.

There is a clear need to recruit more PhD and post doctoral staff to this team. Recently recruited staff should be encouraged to obtain their HDR so that the potential to supervise greater numbers of PhD students within the team can be realised. Staff should also be ecouraged to use their international collaborative links to attract post doctoral staff from abroad on self funded fellowship programmes.

It is unclear whether the team's activities have been contrained by the resource that has been allocated to it over the past four years and whether it might restrain growth and development of the projects described in the future. The team acknowledges the difficulties associated with lack of funding, and consequently needs to be more prolific in exploring potential funding sources (national and international) that could be "tapped" either independently or as part of a multi-centre collaborative venture. There are also significant opportunities for newly recruited staff to apply for new investigator awards and, where possible, those who have generated findings of significant impact should be nominated by the JRU management or team principal for research excellence awards run, for example, by learned societies. Such recognition will not only elevate their own scientific standing, but raise the international profile of the team as a whole.

Team 6: Micronutrients and cardiovascular health

Leader: Mr. André MAZUR

- Staff members

	Past MiMES	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	7	6
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	11	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	8	7
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 2.8 of the application file)	5	
N7: Number of staff members with a HDR or a similar grade	7	4

- Appreciation of the results

The main topic of this team is to understand the mechanisms by which plant bioactive compounds can contribute to a protective effect against degenerative diseases with a particular emphasis on cardiovascular diseases. The studies involve in vitro models, animal models and clinical studies. Among the results obtained during the reporting period, the team has developped new "omics" approaches (food metabolome) concerning the effect of various nutrients on the complex metabolite profile which is generated. It allows to identify "biomarkers" of a specific nutrient consumption. Generalization of this kind of study should allow to have a precise idea of individual food composition which is presently mainly based on a posteriori questionnaires. An exhaustive database for the polyphenol components of food was also developed which gathers the polyphenol species content of more than 450 food products.

From 2006 to 2010, the team consisted of 9 permanent researchers, 8 ITA, 11 post-doctoral fellows and 10 PhD students. The achievements of the team over the last 4 years have been significant, with 133 publications mainly in the field of “nutrients” and in the top nutrition and nutrient related pathologies journals, Am. J. Clin. Nutr. Atherosclerosis, Eur. J. Clin. Nutr.; J. Nutr.; Brit. J. Nutr). These publications in indexed journals include 29% with impact factor between 3 and 6 and 5% in journal with impact factor between 6 and 8 (in addition to one collaborative article in Nature Genetics IF> 20).

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

The team leaders have numerous external requests from conferences (47 invitations, 38 in international congresses) and communications (240). Involvement in dissemination of knowledge is high: 22 review articles in international journals, 7 book chapters and the editing of a book. The team leaders are internationally recognized as experts on nutrients and are very active internationally (members of organizing committees and scientific committees of national and international congresses and conferences), making the group attractive for students, post-doctoral fellows and visiting scientists. The team has also filed 1 patent, obtained numerous funding grants from a multitude of different sources: National (8), European (4), International (2), industrial contracts (5) in addition to 5 grants from INRA.

- Appreciation on the scientific strategy and the project

This is a large team that will refocus its goals, in particular on the role of micronutrients on the maintenance of cardiovascular system functions and in the prevention of cardiovascular disease. The main scientific topics that combine basic and applied research include investigation into the impact of micronutrients 1) on endothelial dysfunction; 2) on chronic inflammation; 3) on the oxidative stress status, predominantly in animal models but there will be also clinically-oriented projects. The objectives are to determine the role of dietary nutrients in vascular protection and to identify the mechanisms of their action on vascular cells. The oral and written report did not clearly highlight the overall strategy that governed their choice of nutrients (PUFAs, polyphenols, metabolites, vitamins, minerals and cocktail of nutrients) as the possibilities are infinite. Equally, the endpoints are numerous (nutrigenomics, transcriptomics, metabolomics, microRNA, oxiproteome, functional genomics), in addition to the vascular components targeted (endothelial cells, immune cells). The choices have not been closely connected and there is a risk of superficial studies. The team should clearly identify "hypothesis-based questions" with a strong rationale that will govern the choice of the most pertinent endpoints, models and tools. This should enable publications of the highest level.

- Conclusion :

  - Summary

The team has already built the tools, database and a good knowledge of micronutrients which is needed in order to conduct its new projects, as attested by the recent bibliography. The team has also good expertise in the bioavailability and metabolism of micronutrients that should facilitate the settlement of preclinical and clinical studies in order to determine their health effects.

  - Strengths and opportunities

The team is well balanced in terms of the number of researchers and of technical personnel with many students and post-docs. The team is recognized in the field of micronutrients and is renowned for its expertise. The team is actively involved in national and international projects (including EU projects) and collaborative networks of excellence, which should favor creative, collaborative research. The team is developing its expertise on pre-clinical and clinical trials of nutritional interventions using volunteers, with the capacity to explore vascular function.

  - Weaknesses

The oral presentation did not communicate a clear understanding of the projects, complementary skills and respective roles of the team members. The proposal appears broad in terms of selection of micronutrients and their metabolites, therefore it seems important to the committee that the group also focuses on questions where it has the chance to make original and in-depth contribution to the field. The committee pointed out some future concerns with the governance of a large team and the necessity of facilitating the emergence of future leaders.

  - Recommendations

Overall the team has the critical mass to balance its research between its actual expertise (screening for micronutrients and their impact on surrogate markers of cardiovascular disease) and the development of more hypothesis-based science. This might imply to structure more clearly the projects and to focus on a limited number of topics.

The team has shown its potential to publish regularly in the most renowned journals in the field but should try equally to publish in higher-impact non-specialized journals, even if this would result in an overall quantitative decrease in the number of low IF publications. Given the number of group members, a young team leader or deputy team leader would strengthen the organization of the team.

Team 7: Control of lipido-energetic homeostasis and obesity

Leader: Mrs. Béatrice MORIO

- Staff members

	Past MLE	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	0	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	5	4
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 2.8 of the application file)	3	
N7: Number of staff members with a HDR or a similar grade	3	5

- Appreciation on the results

The main topic of this team during the reporting period was to understand the role of lipids in human nutritional pathologies and to provide energy needs evaluations. Among their most interesting results is the fact that trans-MUFA of natural origin are less deleterious in terms of cardiovascular risk than trans-MUFA of industrial origin in humans and that addition of the formerin dairy fat has some protective effect. Trans-MUFA whatever their origin do not seem to be deleterious for insulin sensitivity. They have also shown that obesity is not concomitant with a reduction in muscle mitochondria number but with their oxidative capacity. Finally they have shown that in Parkinson patients, the body weigth gain which is seen after chronic subthalamic bilateral stimulation is due to a decrease in energy expenditure.

The topic is interesting since most of the studies deal with human nutrition and associated pathologies. The strength of the team is to associate human clinical studies with well conducted nutrition studies. In addition, it is in line with the orientations given by the human nutrition department of INRA concerning the role of nutrition for human health.

75 papers have been published since 2006 and 27 originating directly from the team members. For the later, the mean impact factor is around 3 with some top journals of the field such as JCEM, Am J Clin Nutr (2 papers), J. Lipid Res, Brain, Journal of Nutrition, FASEB J. The team leader has published 9 papers as last author. Globally, it is a quantitative and qualitative good production but considering the numbers of full time researchers in the team, publication in top journals could certainly be still improved. It is a pity that the number of mechanistics studies forming the basis of hypotheses to test in humans remains weak.

Three PhD thesis and one HDR have been achieved during the reporting period.

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

Team members have been invited to a dozen of international conferences. They have been members of several expert committees (AERES, AFFSA, ANSES...). They are sollicited for manuscript reviews in numerous international journals including high standard ones (Diabetes, Diabetologia, Am. J. Physiol) and have been part of the jury of 17 thesis and HDR.

They have hosted or are hosting 6 PhD students, two french post-docs and 10 master students. They are members of 2 EU funded networks and are participating to an EU FP7 "NuAGE" research contract. They have obtained 5 ANR (PNRA) one PHRC, a grant from AFM and one from the french society for diabetes. The team is collaborating both at the national and international level and has 9 industrial partnerships. They have one patent. They have been also extremely successful in fund raising at a national and regional level, 5 ANR-PNRA, 5 PHRC (as participants). They have many national and international (New-Zeland, USA (3), Netherlands) collaborations.

They have thus a very good national and international recognition and are very active in terms of fund raising and socioeconomic partnerships.

- Appreciation on the scientific strategy and the project

The main projects deal with the description and control of energy balance, including the development of specific tools to appreciate in humans energy expenditure and the potential role of physical activity and specific nutrients on this balance. Skeletal muscle dysfunctions and the role of inflammation and lipids will also be addressed. The topics are important since they address main pathologies linked to nutrition, obesity and insulin resistance.

However, it was difficult from the written document as well as from the presentation to have a clear view of what will be really done.

The program does not indicate on which models (cohorts, animals, cells...) the various studies will be performed, especially when considering mechanistic studies. In addition, the number of ongoing projects is clearly too high for the group. As mentioned above, whereas cellular and molecular studies are necessary to support more clinical studies (as recognized by the Pi) there is no clear plan to achieve this goal except for the arrival of an assistant-scientist. Insulin resistance in muscles is a very competitive field and it is difficult to identify what will be the specifity and opportunities of this group allowing to publish high quality papers. They want also to develop a program on mitochondrial metabolism but up to now they have no experience of the field.

- Conclusion :

  - Summary

This team has done a good job during the last reporting period and has achieved national and international recognition. It has been extremely efficient for raising funds and develop socioeconomic partnerships and questions. The emergence of a new leader should be an opportunity to develop more mechanistic studies, to further upgrade the quality of publications and to focus the ongoing research on the most promising subjects.

  - Strengths and opportunities

The team has an extremely good knowledge in the nutritional field and their capacity is recognized at both a national and international level. They have developed interesting tools for human studies on energy metabolism and they benefit from a strong technical help as well as from a number of external financial ressources. They have set up close collaborations with clinical teams and especially the CRNH of Clermont-Ferrand.

  - Weaknesses and threats

The team has up to now no real expertise for cellular and molecular studies and they are very much dependent on collaborations including with potential competitors. There are too many subjects and this does not allow to perform a more vertical approach.

  - Recommendations

The most important recommandation is undoubtly to focus on a small number of projects in order to be able to develop mechanistic studies. They must define what will be their specificities in the field and recruit post-docs in order to help them to develop cellular and molecular approaches. This is the only way to publish in top journals in the field of clinical studies. They could possibly alo slightly limit their industrial partnerships and try to obtain more academic financing (EU projects, ANR blanc ...).

Team 8: Bioenergetic Metabolism and Modelling (MBM)

Leader: Mr. Georges STEPIEN

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	0	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
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 2.8 of the application file)	1	
N7: Number of staff members with a HDR or a similar grade	4	4

- Appreciation on the results

This team was created in october 2008 with researchers coming from either an INSERM Unit (JRU 484) or Clermont1-University. Its specific activity actually started in january 2009. In the past 4 years, these researchers worked on different cellular models but with the same main topic, the study of cellular metabolic changes linked to cell transformation and anti-carcinogenic agent (CENU) treatment. The major contributions are (i) the analysis of mitochondrial bioenergetics and metabolic profile evolution during the cell transformation in absence or in presence of an anti-carcinogenic agent ; (ii) the characterization of the main role played by glutaminolysis when the melanoma escapes the treatment ; (iii) the construction of promotology sofware for the analysis of gene expression results and gene regulation databases. An application of this GeneProm sofware allowed the development of a phylogenetic analysis of the 4 genes coding for the ANT and to identify, from the promoter structure study, different genes that are co-regulated with each of the 4 ANT isoforms. Since 2006, the researchers of this team have published 14 papers in specialized peer-reviewed journals, 10 of which are primary work of the team members. However, most of these publications are not in high impact journals (only 3 of them have an IP higher than 4). The team members have regularly presented their work as oral presentations at international and national conferences. Georges Stepien was the main organizer of the annual congress of the French society for biochemistry and molecular biology in september 2006. One thesis has been defended during this period.

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

The team members have given 2 invited lectures in international congresses and 5 oral communications in international meetings. Two fundings were obtained: LifeGrid 1 European Project (2006-2008) and CLARA ProCan Project (2009-2010). Since the creation of this team, an interesting network of collaborations was strengthened with the “Laboratoire d’informatique de l’Ecole Polytechnique”, the “Laboratoire de Biochimie et de Biologie moléculaire” (INSERM U694, Angers), the “Laboratoire de Neuro-oncologie de l’Institut des Neurosciences” (INSERM U836, Grenoble) and a local bioinformatic company (Soluscience). These collaborations are absolutely necessary for an efficient development of the bioinformatic processing of all the data obtained by metabolomic, transcriptomic and analyze of transcription regulation mechanisms.

- Appreciation on the scientific strategy and the project

This small team proposes a very ambitious project which is the study, by high-flow technologies and modelling, of the contribution of some nutritional factors on the appearance and the development of human hepatic pathologies (i.e. steatosis, fibrosis and cirrhosis). This project could be of interest and fits with the general scientific strategy of the unit. The strategy of the team is to identify from a huge amount of data obtained by gene regulation analysis (promoter strategy analysis), transcriptomic, metabolomic and proteomic the major changes in the bioenergetic and metabolic pathways during the different steps of pathologic development. This requires the development of new software packages that will allow the modelling of the modification of cellular metabolism in response to the advance of a specific pathology.The final goal is to be able (i) to identify targets of therapeutic interest and (ii) to adapt nutritional diet either for prevention or, together with pharmacological treatments, to improve the early therapy. Even if the researchers involved in this project and the surrounding unit scientists have some skills in large scale exploration of cellular metabolism and in molecular biology, the objectives seem unrealistic for such a small group which does not possess the necessary skills in bioinformatics. The different steps in producing the data are described but the methodology used to combine and integrate knowledge from the different experiments (i.e transcriptomic, metabolomic, proteomic) lack precision. In addition it is questionable whether it is the mission of biologists to develop such softwares.

- Conclusion :

  - Summary:

This small team proposes an ambitious project which is interesting and well integrated in the scientific strategy of the unit. However, the team size is too small and the feasibility of this project in 4 years seems very weak. The past production is below what it should be for such an ambitious project.The project has to be more focused for instance on the study of patients and on the construction of an efficient model. The project requires additional fundings as well as additional strengths in bioinformatics.

  - Strengths and opportunities:

The team can rely on the quality of the local metabolic platform and on the complementary skills of the team members. The collaborations are well chosen particularly with the “Laboratoire d’informatique de l’Ecole Polytechnique”. In addition, there is a real need in the scientific community for developments in modeling tools in order to integrate metabolomic, transcriptomic and signalling data.

  - Weaknesses and threats

The size of the team is not in adequation with the project. The lack of technical support and of true specialists in bioinformatics is a clear weakness all the more as many teams worldwide are working on these bioinformatic challenges. The project is too wide. The autonomy of the team members to build the software and to perform all the proposed tests is not established.

  - Recommendations:

The project must be much more focused and the timing strongly defined in order to obtain high quality results allowing to prove its long-term feasibility. In this respect, the vailidity of the project will require additional strengths in bio-informatic. Finally the team must make an effort to increase its attractivity (high quality publications, fundings, post-docs...).

Team 9: Cell microenvironment, immunomodulation and nutrition

Leader: Mrs. Marie-Paule VASSON

- Staff members

	Past EA 4233	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	17	15
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 (Forms 2.2, 2.4 and 2.7 of the application file)	7	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	9	4
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 2.8 of the application file)	8	
N7: Number of staff members with a HDR or a similar grade	11	9

- Appreciation on the results

This team (EA4233, Nutrition, Carcinogenesis, anti-tumor therapy) was a rather large team during the reporting period and was affiliated to the Université d'Auvergne. The research activiy of the team was focused on three complementary topics: nutrition and breast carcinogenesis, nutrition and tumor therapy, and nutritional immunomodulation. These research areas were addressed using approaches at the cellular level, in animals, as well as in humans in the context of clinical studies.

The relevance and clinical interest of these topics are high as they aim at identifying nutritional approaches to potentiate conventional treatments for cancer and inflammatory diseases. The studies conducted by the team during the previous four-year contract have notably demonstrated the interaction of phytoestrogens and adipokines with the expression of genes regulating apoptosis and cell proliferation. The “Nutrition and anti-tumor therapy” group, has demonstrated the importance of the metabolic fate of arginine in the induction of the tolerogenic response to photo-chemotherapy. Finally the “Nutritional immunomodulation” group has shown a protective effect of various polyphenols in the context of an experimental inflammatory disease in animals. This protective effect is mediated, at least in part, through the modulation of both lymphocyte proliferation and antioxidant defence systems.

The number and level of publication of this large team is reasonably good: 101 research articles published since 2006, half of them originating directly from the team members. There are 3 articles in the top 10 journals of of Nutrition and Food research specialties and 5 articles in scientific journals with a higher impact factor but for the later, only one originates directly from the team members.

The team has filed 5 patents on the topic of cancer. Six PhD were supported in the team over the last 4 years, with 2-5 international publications or patents for each PhD student.

The team is a recognized part of the “CRNH Auvergne” and its research topics are in line with the policy of the "Cancéropôle Lyon Auvergne Rhône Alpes", in connection with the Centre de Lutte Contre le Cancer (CLCC) "Jean-Perrin". Through these federative structures, it maintains close contractual relationships with local authorities, which provide significant budgetary resources and opportunities for scientific and clinical collaborations.

- 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 presented 15 communications as invited speakers in congress in France (7) or abroad (8).

Over the evaluated period, the team has recruited three foreign postdocs for periods of 3 to 6 months (Mali and Côte d'Ivoire), a French post-doctoral fellow (Clermont-Ferrand) for a period of 1 year and 6 ATER for periods ranging from 1 to 3 years. The unit head highlights the difficulty of obtaining financial support to host foreign postdoctoral fellows and joint PhDs.

The total budget of the team is on the order of 400 000 Euros per year. The funds are provided for only 7% by the home institution (Université de Clermont-Ferrand) and for 14% by Europe. The remaining 79% are supplied by contracts from diverse origins (Associations, ANR, industrial services, etc ...).

The team has developed collaboration at the national, inter-regional and regional levels. Indeed, the research topics developed by the unit are within the guidelines of the Centre de Recherche en Nutrition Humaine d'Auvergne (CRNH-A) (Axis "Hormonodependant tissues") and the Procan program of the Cancéropôle Lyon Auvergne Rhône Alpes (CLARA) (axis "Nutrition, Metabolism and Cancer"). The team was one of the partner of the ANR contract "Compalimage" in 2005 (PI : MP Vasson); of the European project "AquaMax" in 2005 (PI: MP Vasson), and was the leader of an Inter-regional project (INEC) in 2005 (PI: MP Vasson).

The axis "Oncology" has important potential clinical applications, as evidenced by 5 patents filed by the team over the evaluated period. Moreover, all the research topics of the team had a potential for industrial development since several companies have contributed to the research funding (CIFRE 2008-2010 with Biosphere 99; contracts with Novartis, Pierre Fabre, Nestle and Naturialys).

- Appreciation on the scientific strategy and the project

This team will be a novel one in the JRU 1019, allowing to address new topic in the field of clinical nutritions.

After the reorganization of the team, five researchers (3 PU-PH and 2 MCF), 2 physicians (PH), 3 engineers (IGR), and 1 technician (IGE TCH) will join another unit. In return, the team will gain three new researchers (1 MCU-PH and 2 PU-PH) and 1 physician (PH). The research project is divided into two axes: "Cell-cell microenvironment interactions" and "Nutritional immunomodulation". In terms of human resources, the team is divided into 5 sub-groups of 3 to 7 people each, working in five distinct structures in the same building. In addition, the division into 5 sub-groups indicates an imbalance in the allocation of technical staff (2 of the 5 sub-groups have no technical FTE). It would be particularly desirable to promote a rational combination of staff and resources.

Three research projects are described for each of the two research axes of the team.

The projects of the "Cell-cell microenvironment interactions" axis, which are a continuation of the work of the EA 4233, are realistic. However, most of their potential clinical opportunities remain in the field of oncology (role of adipocytes in the development of breast cancer among postmenopausal women; role of adipose tissue in the control of the antitumor activity of NK cells; aberrant glycosylations and dendritic cell dysfunction in lung cancer). The current configuration of the team does not show any clinical expert in the field of nutrition and cancer and it is likely that the clinical research of this axis will lose effectiveness. For example, the 5 patents issued over the previous four years by the EA 4233 were in the field of oncology and all the authors of these patents will have left the team in its new configuration.

The 3 projects of the "Nutritional Immunomodulation" axis are also in line with previous studies (Polyphenols and prevention of colonic inflammation; immunomodulatory properties of probiotics; pharmaconutrition associated with therapy and/or vaccination) and are of very promising research areas. In addition, 2 PU-PH and 1 PH will reinforce the team in the specialties of immunology and vaccinology.

The team has demonstrated over the past years, its ability to obtain financial supports and the allocation of the budget was balanced (19% for equipment, 20% for HR and 61% for operations and miscellaneous expenses).

Most of the proposed programs are in line with previous works of the team and do not represent special cutting edge projects except perhaps the project dealing with pharmaconutrition and vaccines in the elderly, which is more original and innovative. However, the involvement in the team of expert clinicians in immunology and vaccinology provides guarantees of success.

- Conclusion:

  - Summary:

The research axes defined by the team "Cell microenvironment, immunomodulation and nutrition" fit within the overall objectives of the unit JRU1019. The research programs that have been conducted over the past years are translational and the scientific output is reasonably correct both quantitatively and qualitatively. However, the team will have to make a special effort to maintain its production in the field of clinical applications (patents), as the investigators who were leaders in this area will join another unit for the next contract. In addition, this still large group should aim at publishing in high impact journals.

  - Strengths and opportunities:

The team has demonstrated its ability to find significant financial resources from the Cancéropôle Lyon Auvergne Rhône Alpes (CLARA) and has good opportunities for collaborations in a scientific and clinical context. Moreover it has developed fruitful relationship with industry over the past years and collaborative work with the temas from INRA. Finally, the recent integration of experts in immunology and vaccinology might allow the emergence of new original projects.

  - Weaknesses and threats:

The organization of the team in 5 sub-groups is not justified on a thematic level. In addition, the scattering of the researchers and the poor distribution of the technical staff weakens the scientific cohesion of the team.

The research staff is strongly involved in teaching and/or clinics and the team lacks full-time researchers to ensure a link between the different projects and approaches, and improve the overall level of publication. The new organization of the team represents a risk of weakening the potential of clinical development in oncology, due to the departure of several cinical experts.

  - Recommendations:

The committee recommends combining the five sub-groups to improve the scientific consistency of the team. In addition, the team will have to assert its scientific reputation through high standard publications, signed by members of the team as first and/or last authors. It might be also important to facilitate the emergence of future leaders.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
UNITE DE NUTRITION HUMAINE	B	A	A	B	B
PROTEOLYSIS [CHARDIGNY-ATTAIX]	A	A	Non noté	A+	A
NUTRITION, METABOLISM AND MUSCLE LOSS [CHARDIGNY-BOIRIE]	A	A	Non noté	A	A
INTEGRATED METABOLISM, METABOLOME AND NUTRITIONAL BIOMARKERS [CHARDIGNY-COMTE]	C	B	Non noté	B	B
FOOD, SQUELETON AND METABOLISM [CHARDIGNY-COXAM]	B	A	Non noté	B	B
ADAPTATIVE MECHANISMS TO NUTRITIONAL STRESSES [CHARDIGNY-FAFOURNOUX]	A	A	Non noté	A+	A
MICRONUTRIENTS AND CARDIOVASCULAR HEALTH [CHARDIGNY-MAZUR]	A	A	Non noté	B	A
CONTROL OF LIPIDO-ENERGETIC HOMEOSTASIS AND OBESITY [CHARDIGNY-MORIO]	A	A	Non noté	B	A
BIOENERGETIC METABOLISM AND MODELLING [CHARDIGNY-STEPIEN]	B	C	Non noté	C	C
NUTRITION; CANCER, ANTI-TUMOR THERAPY [CHARDIGNY-VASSON]	B	B	Non noté	B	B

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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Clermont-Ferrand, le 8 juillet 2011

Le Président

et

Le Vice-président du Conseil Scientifique

à

Monsieur Pierre Glorieux
Directeur de la section des unités de recherche
AERES
20 rue Vivienne
75002 Paris

OBJET : Rapport d'évaluation S2UR120001955 – UNH : Unité de Nutrition Humaine – 0631262E

Direction de la Recherche

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N/réf. :DR-IR/AL/2011 N°216

Monsieur le Directeur,

Je vous prie de bien vouloir trouver ci-joint les observations de portée générale concernant le rapport d'évaluation de l'unité « UNH » dirigée par Jean-Michel Chardigny, envoyé le 6 avril 2011, observations que j'approuve bien évidemment.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de mes sentiments les plus cordiaux.

Professeur Philippe Dulbecco
Président de l'Université d'Auvergne

Professeur Alain Eschalier
Vice-président du Conseil Scientifique

REPUBLIQUE FRANÇAISE
INRA
INSTITUT NATIONAL DE LA RECHERCHE AGRONOMIQUE

UMR 1019
UNITE DE NUTRITION HUMAINE

UNIVERSITE D'AUVERGNE
CLERMONT-FD1

Comments on the AERES report on the research "Unité de Nutrition Humaine" from the Université Clermont-Ferrand I and INRA

General comments

The JRU management and staff acknowledge the committee and the observers for their strong input in the evaluation process and the report. This report underlines some strengths and weaknesses and suggests several suitable recommendations. However, we deeply regret the lack of an expert on integrated nutrition, especially with regard to the last-minute withdrawal of one of the committee members.

The dispersion of the topics has already been reduced in the past years. The teams are now more focused on 4 health targets (sarcopenia, osteoporosis, metabolic syndrome and vascular dysfunction) rather than on studies of specific nutrients. The JRU project is the result of an important collective reflection carried out during more than one year. This strategy will be continued during the further 5 year period, having both targeted and integrated (multi tissue/functions) approaches.

Bioinformatics is a key factor for the success of the project. However, the bioinformatics staff, which belongs to the IbIsA upgraded Platform for Metabolism Exploration (PFEM), was not concerned by the present evaluation (considered as a tool and not a scientific question). Hence, the committee had no entire possibility to realize our actual capability in this area. Moreover, extended partnerships on this respect are currently built, thanks to the "Investissement d'Avenir" calls.

More in-depth research is a constant challenge for our unit. Most of the teams cover their topics from basic research to preclinical/clinical studies. Effort will be done to better focus on more specific topics and promote a mechanistic research.

International funding and attractiveness: The objective for the further 5 years is to extend our participation to EU projects. In this respect, participation to a ITN

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application is under evaluation. Specific meetings have already been organized and will continue on our contribution to the next EU call (Nutrition area of the KBBE call) and proposition of further topics for future calls (in relationship with national contact points and persons in charge of EU projects from the INRA and University).

Some changes between the written report and the oral presentations have not been taken into account by the evaluation committee, this in particular for the team 3. It has been stated in the written report that a senior scientist (DR2) from this team left the unit in December 2010. Despite this weakening of this team, its creation was affirmed by all INRA management levels, considered this as an important challenge for the nutrition research in our institute. It is also important to underlay that the research carried out by this team is closely based on technical support (mass spectrometry and informatics) of the Platform for Metabolism Exploration (PFEM) (not evaluated as stated ahead).
Specific comments are also included below (see the team 3 section).
Moreover, we regret the lack of harmonization of the evaluation process between the teams (different criteria being considered).

Adjustments to make taking into account the comments of the commission, including the future of the weakest teams will be discussed with INRA and University.

Other minor remarks
University was represented not only by the President, but also by Alain Eschalier, Vice Head of the Scientific Council and Patrice Deteix, Dean of the Faculty of Medicine
In the introduction section, "…the committee listened to the presentations from each of the **teams**." Jean Fioramonti was not a local but a national representative of INRA.

Specific comments

Team 1 (Proteolysis)

The Proteolysis team thanks the committee for its constructive comments. The lack of post-doc in the team is due to budget constraints. However, we have recently applied for a post-doctoral position at the CPER and will certainly apply more frequently for such funding when available. Another limitation is the lack of a Biacore on site although we have

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been repeatedly asking for funding. The recommendation concerning publication in high standard journals is already followed, one paper being currently in revision in such a journal.

Team 2 (Nutrition, Metabolism, Muscle Loss)

The team thanks the reviewers for their constructive comments and appreciation on the activity and projects. Some weaknesses and recommendations have been noticed by the evaluation committee.

We totally agree with the comment about novel molecular mechanisms. Collaborative exchanges have been recently established with basic scientists from CNRS and INSERM (Thérapie des maladies du muscle strié / Institut de Myologie UMRS 974 - UPMC Univ. Paris 6 / U974 - Inserm / UMR7215 - CNRS-AI, Paris, CNRS UMR6247, Clermont Université, INSERM U931GReD, Clermont-Ferrand and CNRS/INSERM ERI21-EA4319 Inflammation et Carcinogenese UFR Medecine, Nice) addressing molecular mechanisms in the field. In the next future, as highlighted by the members of the committee, a global consequent budget from academic and industrial funding has been already secured. A part of this budget will be directed toward developing new techniques and models to explore innovative aspects of muscle aging. For example, non-protein nutrients such as n-3 PUFA or vitamin D are nowadays considered as strong regulators of muscle anabolism. However, their molecular and cellular mechanisms of action in muscle tissue and the change with old age are still enigmatic. Therefore, we plan to establish new research programmes considering these innovative concepts by using either cultured muscle cells, new animal models (e.g. KO VDR mice), and clinical investigation. Other collaborative projects have been also established with scientists from Inserm in Nice and papers in press are related to basic aspects of signalling pathways in response to amino acid changes.
New concepts have already emerged from our team, e.g. the specific anti-anabolic effect of reactive lipid intermediates in aged muscles and their mechanism of action in muscle cells. We are now in the way to publish these new data in a high ranked general journal such as J Clin Invest or Aging Cell.
A permanent position for a qualified research engineer with expertise in cellular biology and molecular biology has been opened last year. This new collaborator has in charge to develop techniques to measure protein synthesis rate in cultured muscle cells and to

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explore molecular pathways in muscle tissue. The technical development will continue in the team and we will try to reinforce this aspect by asking for a new position for a researcher with expertise in this field in the years to come in conjunction with new technical supports.
To sum-up, we are aware that the know-how and the large size of our team should allow developing cutting-edge projects. We are very interested in these aspects, and we will concentrate our scientific strengths to provide mechanistic insights that will increase the knowledges in the field of muscle mass loss to prevent it in situation where sarcopenia occurs.

Considering post doc attractiveness, as reported in the committee comments, we have got important funding to work on several interconnected aspects of muscle anabolism variation with aging. With these budgets, we plan to hire at least 2 qualified post-docs with new expertises in 2011 and 2012. These new expertises, i.e. on usual and cutting-edge molecular and cellular techniques, together with the current intrinsic technical development will allow us to set up relevant models to address more deeply our scientific questions. These post-docs should be found on the basis of our multiple connections with other international teams in the field of Muscle Metabolism.

Team 3: (now Metabolic Phenotype and Preventive Nutrition, PMNP);

The project for the PMNP team creation was decided, as the priority for the JRU, just before starting the preparation of the evolution report (mid 2010). Since this decision, one DR2 left INRA (December 2010) and the team was reinforced by one CR2 (December 2010). In this context, the written project has matured and been refocused for the oral presentation.

We have to stress that some important concerns do not have been fully integrated by the committee and are listed below along with complementary information.

A – Scientist evaluation

1 - The efforts invested by the team leader over the last four years for the development of a cutting-edge approach on integrated metabolism using metabolomics have significantly contributed to:

- An important evolution of the scientific project of the research unit,

- The adhesion of researchers in the JRU to this approach concretised into several collaborative projects,
- A greater integration of the JRU in existing national and international metabolomics networks (RFMF, NUGO) and building of new networks (ITN, consortium for an EU project).

All these achievements were not visible in the written document. However, the capacity of the PI to lead the project cannot be considered only on the basis of the number and/or impact factor of publications in such new evolving field. Her strong expertise in metabolism and mass spectrometry is a crucial strength for the success of the team's project; more important than bioinformatics skills that can be obtained through collaboration (see below). Her recent invitation to an international metabolomics meeting shows that her expertise has begun to be recognised.

2 - The contribution of IE, recently promoted to IR, has not been integrated in the scientific evaluation, while today she is a widely recognized scientist on the phytochemicals and metabolomics fields: H index = 30, HDR, expertises at ANSES and EFSA, invited lectures. Her Food metabolome-related production includes a review paper, 4 invited lectures and 3 oral communications in international conferences, the coordination of the ANR PhenoMeNep project (see below), and a science prize at the 6th European Nutrigenomics conference (2007). Her acquired skills and the tools she has developed for metabolomics analysis and data treatment constitute one of the major strengths of the team to develop the proposed projects.

B – Results

We realized that some contributions of the team members to the former MiMeS team ('overview of results (2006-10)' in the Assessment booklet p.43-50) were not considered during the evaluation process of the PMNP team.

C- Attractiveness

We would like to highlight some relevant information that the committee could have missed in the written document (administrative booklet, p.14-16):

- *Students and post-doctoral fellows*: during the reporting period, the Pi and the IR have supervised: 2 PhD students, 3 post-docs (2 foreigners: Spanish, German) and 6 foreign students (Spanish, Dutch, Belgian, and Polish); about half of them have worked on metabolomics related projects. Currently, one co-supervised PhD student and three post-doctoral fellows are involved in the team project. The team has been involved in the creation of a Marie-Curie Initial Training Network for metabolomics.

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- *Contribution to organisation and scientific boards of meetings on metabolomics and nutrition*: 1st NuGO workshops on 'Tools and methods for mass spectrometry Metabolomics in Nutrition' 2007, 2009; 5th International Conference on polyphenols and health, 2011; 2nd International Congress on Translational Research in Human Nutrition, 2012.

D – Research project

The project PhenoMeNep, coordinated by the IR has been funded. In this context, non permanent personnel were incorporated to the team, including two post-doctoral fellowships and one Master 2 bioinformatics' student.

The team's project has been refocused on 2 axes, one on metabolic phenotyping and the role of nutrition, and the other one on Food metabolome.

E - Models and tools

Bioinformatics.The objective of the team regarding metabolomics is to use and improve this promising approach for its scientific questions, but not to develop statistical and bioinformatics methods and tools. Several important bio-informatics groups in the world are currently doing those developments for metabolomics. The strategy of the team is to participate in international networks in which these tools are shared, in order to regularly update its methods. We are strongly supported on this aspect by the statistician and the bio-informaticians of the UNH mass spectrometry platform (PFEM).

Furthermore when needed for research projects, collaborations with bio-informaticians can be build. For example, the team is collaborating with the world leader group in databases for metabolomics (Univ. Alberta) in PhenoMeNep. Although the strengths could be valuably reinforced in the platform, this has not been a limiting factor in obtaining innovative results on the Food metabolome.

Biological resources. The scientists of the team have a wide experience in animal handling and experimentation (rodents, fish, dogs, and chicken) and can develop their own protocols in the UNH animal facility. However, we are collaborating with other teams when they have models of particular interest for our research.

The main objective of the Food metabolome approach is to provide tools and biomarkers for epidemiology. Large human cohorts are developed by epidemiologists and the access to samples for particular purpose is negotiated in the context of collaborative projects. Epidemiologists are currently very interested by the approach and opened to collaboration.

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Nutritional intervention studies on small numbers of volunteers can also be performed with the CRNH or the CIC facilities. The team members have already performed such studies.
Therefore the dependency of the team for external biological resources is reasonably limited.

Conclusion
Despite of the uncommon origin and background of the three scientists of the team, their complementary in terms of metabolism and mass spectrometry, physiology and endocrinology, and micronutrients and metabolomics are keys for an integrated understanding of the role of nutrition in disease prevention.
As a whole, although we are aware that for an optimal development of the current project the reinforcement of the team with new permanent members (especially one IE with skills in mass spectrometry data analysis) is mandatory, we would like to emphasize also that the scientific objectives of the project have been positively evaluated and validated by the commission.

Team 4 (Food, Skeleton and Metabolism)

Team 4 is grateful to the commission for its positive evaluation of the team. We appreciate the recognition of our "substantial scientific production", national and international attractiveness, legibility and expertise within the field of bone health. In addition we thank the commission for the constructive remarks that will be taken into account for the immediate future, even though the evaluation report seems to suffer from several misunderstandings.

As a matter of fact, regarding the scientific project, it seems the goals have been misunderstood as the main purpose is the set up of an integrative approach for nutritional osteoporosis rather than searching for isolated molecules, even though mechanistic investigations will be focused on lipids and polyphenols.

The commission highlighted the need for "in depth" and "translational" researches. In this way, in our project, two major parts have been developed on lipids and polyphenols mode of action on bone cells. A young scientist has been recruited only 2 years ago to develop cellular and molecular bone biology. Since this recruitment, several abstracts have been

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published and even awarded at bone meetings and publications are either submitted or in progress. Moreover, as the team size is very limited, a new recruitment is planned for this year to re-inforce the "in depth" approaches.

Besides, as far as translational research is concerned, as mentioned in the written report and presented at the visit, the head of the rheumatology department of the University hospital has joined our team since this year, consistency with our implication in several clinical programs. In fact, he is the "enseignant-chercheur" in the staff member table provided in the report held by the commission. Our "translational" approaches will benefit from his input.

Regarding the originality, impact and chance of success of the project, the team was the first one to highlight the bone sparing effect of polyphenols. In the same manner, mechanisms mediating lipids effects on bone have been poorly described and molecular targets investigated within the team are very promising. In this light, our team has demonstrated, for the first time, the implication of a newly described receptor linking lipids to bone remodeling.

Furthermore, we wish to correct some errors, although these points have not been subject to criticism. Indeed, with regards to national grants and as presented during the visit, we are not only involved in one ANR program, but are currently partners in 2 ANR projects and coordinators of the "polivd3" ANR project.
Concerning our involvement in educational training, in addition to the 3 students who got their PhD during the last period of evaluation, we currently supervise 3 PhD students and we will hire 2 more PhD student on CIFRE grants in the next few months.
Finally, our scientific production is even higher than stated in the report that omitted to include one patent and several publications (We have published during the last 4 years 70 articles, 54 with impact factor, instead of 38). Therefore, our team impact factor should rank from 2.7 to 11.06, rather than 6.7.

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Team 5 (Genes and Nutrients)

Team 5 thanks the AERES committee for encouraging us to follow the proposed program. We are aware of the difficulties that may be encountered and that have been raised. We will respond to the main comments.

We agree with the committee that funding limitation might restrain the development of our projects. We currently have two sources of funding: the basic fund from INRA and external grants. As testified by our current sources of funding, we do apply each year to several calls. Indeed, we obtained in the last few years funding from ANR (2 grants- one of which as coordinator), Ajinomoto (3ARP international Japanese grant), ARC ("subvention libre") and FRM. However, this was barely sufficient to manage our ongoing projects. In 2011, we applied to three ANR's Blanc Programme (one of which is managed by the team leader) and one call by the "Fondation Danone". It is true that during the last 4 yr period, all the proposals were managed by the team leader. However, the other scientists of the team are now starting to take over part of this burden. In addition, we would like to stress that the mechanisms we are studying are just beginning to be related to pathologies (metabolic diseases, cancer, feeding behaviours troubles…) explaining why there are very few calls that match our topics. As publication of the emerging projects in the team are about to be published and the patent concerning the AARE-LUC mice are to be held very soon, we hope that they will open new opportunities to attract private companies to be interested in our work and eventually fund our research. We are indeed starting to weave a network able to help us in this task.

We are totally aware that our team does not have enough students and post doc. Until now, the main reasons are our lack of funding and supervisors (HDR). We hope that the measures taken in 2011 to increase our funding will help for that matter. To participate in that improvement, the three young scientists of the team will apply for "HDR" in 2011 and 2012 in order to be able to supervise PhD students. Moreover, we do suffer from our lack of attractiveness due to our lack of exposure abroad. We definitely have to be more present on international congresses in order to develop our networking and exposure internationally. This might participate in breaking the vicious circle in which our lack of funding put us.

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We realize that our internal collaboration within the UNH did not appear really clearly neither in the manuscript nor in the presentation. Yet, we have ongoing fruitful collaborations mainly with team 7 about mitochondrial functions, with the team 8 about promoter analysis and with team 4 about various technical aspects of molecular biology. Indeed, last year, we have applied to a grant call together with CLEHO and ASM. Given the development of powerful tools in our team (AARE-LUC mice for example), we expect our future collaborations with our colleagues of the UNH to be even more extensive.

Team 6 (Micronutrients and cardiovascular health),

Team 6 acknowledges the commission for its appreciation of the quality of our scientific production, of the attractiveness of our team, and of our international and national collaborative networks. We also appreciate that the committee recognizes our expertise in nutrition research and especially in the micronutrient area. Our skills in preclinical as well as in clinical trials of nutritional interventions with the capacity to explore vascular function were underlined.

As mentioned in our written report, the newly organized "Micronutrients and cardiovascular health" team will refocus its research on the role of phytomicronutrients on the maintenance of vascular system function and on the prevention of cardiovascular diseases. However, this refocusing of the new team on the role of phytochemicals in vascular protection did not appear clear enough to the commission. One can imagine that our willingness to take into account the complexity of the food, which is essential in nutrition research, could give the impression of confusion in choosing micronutrients of interest. Note that the project is based on the hypothesis that dietary phytomicronutrients contribute to the prevention of cardiovascular diseases. Consequently, we reaffirm that our goal is to understand the effects and mechanisms of action of phytomicronutrients (mainly polyphenols and carotenoids), and their most important dietary sources (plant foods), in vascular protection.

With regard to vascular targets, our proposal will concern the relationship between micronutrients and endothelial (dys)function and the early steps of atherogenesis (example: interaction between monocytes/macrophages and endothelium). The choice of these targets is based on data from the literature and also on results of our "omic" studies on animal models that have brought into view mechanistic assumptions whose

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understanding have been extensively deepened in vitro by targeted approaches. We are confident in the ability we have and the approaches we choose to produce relevant knowledge to make original and in-depth contributions to the field.

The committee did not find enough precision in definitions of the respective contributions of the members to the presented project. Our choice for the written report was to present a collective project and the members' contribution to the specific themes was only briefly presented orally. The project will indeed be developed using the highly complementary and interactive skills of team members and will focus on two main topics: endothelial function and oxidative stress (considering the inflammatory component) in atherogenesis. With regard to the committee's particular query: A CR1 is in charge of studies on the role of polyphenols in the maintenance and improvement of endothelial function, mainly by means of human intervention studies; another CR1 is studying the molecular mechanisms by which polyphenols modulate leukocyte adhesion and transendothelial migration; A DR2 is interested in the "antioxidant" action of phytomicronutrients, considering interactions between these components within the food matrix; the team leader (DR2) is interested in the modulation of the inflammatory component of atherosclerosis by phytomicronutrients, namely of monocytes/macrophages; a CR1 is assessing the role of the interaction between phytomicronutrients in the cellular redox balance, oxidative PTM of proteins and their effects on vascular cells; finally, a CR2 is conducting complementary studies on the modulation of lipid peroxidation and its end-products by "antioxidant" phytomicronutrients.

As regards the recommendation to publish in high-impact non-specialized journals, it can be said that to be recognized in both basic and applied topics in the nutrition field, there is a need to publish in the most respected journals whose impact factors may not be as high as, for example, some of those in the medical field. However, we also have mentioned in the written and oral reports that we are capable of publishing in high impact journals from more general and non-nutrition fields (Nature Comm, Nature Gen, J Hepatol, Hypertension, Proteomics …).

Finally, the committee pointed out some concerns with the governance of a large team. The team leader is in favour of sharing the governance with a deputy, as in the past within the MiMeS team, to facilitate the emergence of future leaders. Hence, the new team will be co-directed with a deputy team leader.

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Team 7 (Control of Lipido-Energetic Homeostasis and Obesity)

The AERES has enlightened the dynamism of the CLEHO team, its strong collaborative network, its ability to raise national and regional funds and the good quality of its publication production. We appreciate the constructive comments made by the evaluation committee and will attempt to answer to them.

With regards to the number of full time researcher vs. publication rate, we would like to stress that the research engineer of the team has been working full time for 2 years on the valorisation project "ModelHeart" whose results cannot be published before it is patented. However, two abstracts about methodology have been submitted and accepted at ICAMPAM congress (May 2011). One paper is in preparation. The valorisation of "Finder2E" software created to treat and analyse Modelheart data about energy expenditure and physical activity is currently discussed with INRA Transfert for immediate valorisation, especially within the scientific and clinical communities.

We agree with the committee that we need to develop more mechanistic studies to validate the hypotheses tested in human studies and indentify the cellular effectors of the action of bioactive molecules on insulin resistance. Fully convinced of the importance of this orientation, we will combine rodent-based models and cell culture approaches (myotubes) to explore the mechanisms and validate our hypotheses. These combined strategies allow the investigation of cellular and molecular parameters (cell and tissue lipid composition, mitochondrial functioning, protein and gene expression) together with physiologic (glucose and lipid homeostasis, energy expenditure) and anthropometric parameters. Furthermore, they are complementary to our expertise in clinical studies, which involve muscle biopsies to whole body explorations. We already have and will continue to invest on training in applying cellular and molecular tools, which were not the basic skills of the scientific and technical staffs of the team. Of importance, the recent recruitment of a junior scientist will help at strengthening these approaches. Still today, the recruitment of a technician skilled in cellular and molecular biology is urgently required and a position is opened in this respect.

We thank the evaluation committee for the important comment regarding the necessity to focus on a small number of projects. We are fully aware of this need, we have recently

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focalised the team project on skeletal muscle lipid and energy metabolism. We will pursue our efforts and will now work at strengthening our vertical approach, from mitochondrial functioning to skeletal muscle metabolism and whole body physiology. This requires federating the researchers of the team on a reduced number of projects, as suggested by the evaluation committee. The mechanistic studies will be in part built on the team expertise in mitochondrial metabolism (fat oxidative capacity, respiration, ATP and ROS production) which, contrary to the evaluation committee comment, is internationally recognized and valued since 2001 in 19 publications involving scientists from the team as main mitochondrial investigators.

Team 8 (Bioenergetic Metabolism and Modelling)

Team 8 believes that there was some misunderstanding about their project: the team is a group of biologists, including experts in metabolomics, and the project is based on experiments relying on techniques of enzymology, NMR, and mass spectrometry. Our main focus is to study human hepatic metabolic disorders and the effects of polyunsaturated fatty acids in liver cell functions. Our goal is to produce results from these different methods, in particular to identify new biomarkers, but not to develop software. Our bioinformatic studies are done in collaboration for several years with the Polytechnic School from Palaiseau, with the Soluscience Company and with bioinformaticians from the PFEM. The aim of this bioinformatic work is to predict metabolic pathways involved in studied pathologies and to model them. Moreover, we have skills for using specific software, either developed in collaboration (GeneProm and MPSA software) or available on line (Genomatix, Ensembl) and used to carry out our project. Thus, our input in bioinformatics is not to develop new software packages, but to evaluate specific software or to contribute to their improvement.

In the field of NMR-based metabolomics, we are the first team at an international level to profile the cellular and tissue metabolomic footprint with about 30 to 40 identified and quantified metabolites by using an original 2D-based NMR method that we developed.
We have been solicited by the Biological Magnetic Resonance Data Bank (BMRB Metabololomics Website), in June 2010, to provide them with data published in Magn Reson Med 2010, related to several untreated cancer cell types, and in response to anticancer agents and nutritional factors. This witnesses our expertise in metabolomics.

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The commitee stated that one thesis only has been defended during the last four years (2007). We would like to mention that another thesis has been also co-directed and defended in 2009. In addition, two theses will be defended this year, one at the Palaiseau Ecole Polytechnique in June 2011, and the other one by the end of this year.

As regards to postdoctoral grants, an application is about to be submitted for an "Innovation Région" grant to recruit a bioinformatician who will attend the development of the MPSA program package.

Team 9 (Cell MicroEnvironment, Immunomodulation and Nutrition

The 5 identified sub-groups as mentioned correspond to administrative structures but not to the research organization. The team is organized as an unified group developing multidisciplinary approaches based on specific expertise of the personal. The two research programs (Metabolic and functional interactions of the cells with its microenvironment & Benefit/Risk of nutritional interventions with immunomodulatory effects) are associated within this team. These programs include cell cultures, animal models and clinical trials to evaluate cell functions, cell metabolism and molecular pathways to identify the new concept on immunonutrition.

The projects include clinical trials and also *in vitro* and animal studies. Moreover, concerning the project "adipocytes and breast cancer", a number of collaborations have already been performed with clinical teams in Lyon. Three current funded projects with a team of Jean-Perrin Center. New collaborations have already begun with team 7 and the HNRC (N Cano).
In addition, in the field of nutrition and cancerology, the closed relationship with CLARA axis B "environment, nutrition, cancer" will increase the potential of the team.

The new collaborations and financial grants recently obtained will allow us to publish in higher impact factor journals.

As previously mentioned, the research organization is based on specific expertise of the personal. Interdisciplinary approaches will be developed to perform the goal of the team.

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A proposal has been submitted to relocate the team to a common place in the university building which will facilitate the research activities.

Allocating more time in research and employing full time researchers will allow further research potential of the team. Currently 2 full time researchers have been recruited on the Chaire d'Excellence Research Program. In a near future, we expect to obtain a full-time researcher from INRA Institute or other sources.

In the perspective of the emergence of new leader, we are continuously searching to identify future leaders of the team. Presently, the team is managed by the PI with fruitfull contribution with another PU-PH.

Jean-Michel Chardigny

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