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# PNCA - Physiologie de la nutrition et du comportement alimentaire

Rapport Hcéres

► **To cite this version:**

Rapport d'évaluation d'une entité de recherche. PNCA - Physiologie de la nutrition et du comportement alimentaire. 2014, AgroParisTech - Institut des sciences et industries du vivant et de l'environnement, Institut national de la recherche agronomique - INRA. hceres-02032806

**HAL Id: hceres-02032806**

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Submitted on 20 Feb 2019

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

Department for the evaluation of  
research units

## AERES report on research units and interdisciplinary research units

Physiologie de la Nutrition et du Comportement

Alimentaire

PNCA

Under the supervision of the following  
institutions and research bodies:

Institut National de la Recherche Agronomique - INRA

AgroParisTech - Institut des Sciences et Industries du

Vivant et de l'environnement



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

Department for the evaluation of  
research units

*On behalf of AERES, pursuant to the Decree  
of 3 november 2006<sup>1</sup>,*

- Mr. Didier Houssin, president
- Mr. Pierre Glaudes, head of the  
evaluation of research units department

*On behalf of the expert committee,*

- Mr. Luc PENICAUD, chair of the  
committee

<sup>1</sup> The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n ° 2006-1334 of 3 November 2006, as amended).



## Evaluation report

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

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

|  |  |
|--|--|
| Unit name:                             | Physiologie de la Nutrition et du Comportement Alimentaire |
| Unit acronym:                          | PNCA   |
| Label requested:                       | UMR INRA/AgroParisTech                                     |
| Present no.:                           | 0914   |
| Name of Director<br>(2013-2014):       | Mr Daniel TOMÉ   |
| Name of Project Leader<br>(2015-2019): | Mr Daniel TOMÉ   |

## Expert committee members

|          |  |
|----------|--|
| Chair:   | Mr Luc PENICAUD, CNRS  |
| Experts: | Mr Thomas CROGUENNEC (representative of CNECA)<br>Mr Jean Pascal DEBANDT, Paris Descartes University<br>Ms Nathalie DELZENNE, University catholique of Louvain, Belgique<br>Mr Jean Louis NAHON, CNRS<br>Mr Bernard PORTHA, University Paris Diderot (representative of CSS INRA)<br>Mr Yves SCHUTZ, University of Lausanne, Switzerland |

### Scientific delegate representing the AERES:

Mr Jean GIRARD

### Representatives of the unit's supervising institutions and bodies:

Mr Jean DALLONGEVILLE, INRA

Mr Thierry DORE, AgroParisTech (École Doctorale ABIES)



## 1● Introduction

### History and geographical location of the unit

UMR 0914 was set up in 2002. It resulted from the merging of an INRA research unit and the Human Nutrition research and teaching staff at AgroParisTech. This unit is related to the Centre de Recherche en Nutrition Humaine d'Ile de France (CRNH-IdF) and a clinical investigation center at Avicenne University Hospital (Bobigny, 93). The unit belongs to two institutions and their respective departments: the Life Sciences and Health Department of AgroParisTech, the Nutrition, Chemical Food Safety and Consumer Division (ALIMH) of INRA. It is also involved in the Paris-Saclay University project and the unit has also been an active member recently in the implementation of the ALIAS (Aliment, Alimentation et Santé) network, a Labex created as part of the Idex of this university.

### Management team

The unit is managed by a director (Mr Daniel TOMÉ) and a deputy-director. The direction is assisted by a steering committee and a unit committee (all members of the unit). The steering committee meets once a month to discuss the unit's organisation, budget and research activities and its conclusions are then presented to the unit committee. The budget is managed collectively; teams submit project for authorisation by the steering committee, and attribution of a budget line by the deputy director.

Concerning scientific activity, research projects and interactions between teams, any proposals (theses, postdoctoral contracts, permanent employment contracts, research projects, contracts, etc.) received from researchers, teams or senior managers are discussed by the senior managers and team leaders in order to harmonise and formulate proposals, to recommend the allocation of tasks to different teams, and to ensure general conformity with the strategy of the unit. Such proposals are then discussed and validated by the steering committee and teams before being presented to the unit committee.

Some of the group leaders are also scientific managers of the core facilities.

### AERES nomenclature

SVE\_LS4

### Unit workforce

| Unit workforce  | Number as at<br>30/06/2013 | Number as at<br>01/01/2015 |
|---|----------------------------|----------------------------|
| <b>N1:</b> Permanent professors and similar positions   | 11                         | 15                         |
| <b>N2:</b> Permanent researchers from Institutions and similar positions  | 9                          | 9                          |
| <b>N3:</b> Other permanent staff (without research duties)  | 6                          | 8                          |
| <b>N4:</b> Other professors (Emeritus Professor, on-contract Professor, etc.)   |                            |                            |
| <b>N5:</b> Other researchers from Institutions<br>(Emeritus Research Director, Postdoctoral students, visitors, etc.) | 4                          | 4                          |
| <b>N6:</b> Other contractual staff<br>(without research duties)   | 4                          | 4                          |
| <b>TOTAL N1 to N6</b>   | <b>34</b>                  | <b>40</b>                  |



| Unit workforce   | Number as at 30/06/2013 | Number as at 01/01/2015 |
|--|-------------------------|-------------------------|
| Doctoral students  | 11                      |                         |
| Theses defended  | 21                      |                         |
| Postdoctoral students having spent at least 12 months in the unit* | 8                       |                         |
| Number of Research Supervisor Qualifications (HDR) taken           | 2                       |                         |
| Qualified research supervisors (with an HDR) or similar positions  | 12                      | 14                      |

## 2 • Overall assessment of the interdisciplinary unit

PNCA occupies an original niche in the field of integrative physiology of protein metabolism. The unit has overall a very good scientific output and has been quite successful in raising national funding (particularly private funds). PNCA is strongly involved in teaching activities and training of PhD students, thus providing opportunities for attracting the best graduate students in the unit's teams. The review committee was impressed by the quality of the management and thereby the good atmosphere of the unit.

### Strengths and Opportunities

This unit has a good scientific achievement, clearly apparent when looking at the rationale of its objectives and programs, and at the place that the unit is holding in the socio-economic community.

A very good expertise: 1) in the measurement of nitrogen and amino acid use, 2) in animal physiology and phenotyping.

The current director of the unit has a strong international and national position in the field of protein metabolism. He is a strong motor of the unit, and he combines scientific and human qualities and a high dynamism.

The unit is strongly supported by the two institutions INRA and AgroParisTech.

Relationships with clinicians and agricultural research also demonstrate the interest of the programs and results of the unit.

The strength of the unit is based on the strength of its staff and on the cohesion of all the members of the unit where engineers, technicians and students share the enthusiasm and dynamism of the scientists. The review committee has appreciated the cohesion of the unit and the pleasant working atmosphere.

The research unit is strongly involved in teaching and training activities providing influence towards undergraduate and graduate students.

The development of the Labex ALIAS and the Idex (Saclay University) projects although seen as threats by many staff members.

The recruitment of a new Professor can be seen as a strength if this is really open to external candidates and if the project led by the new Professor is in good line with those proposed by the unit.



### Weaknesses and threats:

- Low number of post-docs, especially foreign ones;
- Limited mechanistic approaches;
- A relative lack of public or European funding;
- The retirement of a large number of persons including unit's director and group leaders during or at the end of the next period;
- A geographical dispersion that does not help.

### Recommendations:

Intensify the reflection and the efforts for a better coordination between teams on common projects and for a better coherence on the whole project of the unit. Initiatives should be taken to strengthen collaborations within the unit.

Define collectively within the unit a strategy for improving the attractiveness for new scientists. A call for applications could be launched by PNCA to host researchers with permanent positions that will reinforce potential and open new perspectives.

The international visibility of the unit should be strengthened through different actions including (I) intensification of external collaboration, and (II) recruitment of foreign PhD students and researchers.

The team leaders are encouraged to be more selective and to limit the number of on-going projects.

The current programs and projects may clearly get higher recognition from including more in depth mechanistic approaches.



### 3 • Detailed assessments

#### Assessment of scientific quality and outputs

- Ahead of the site visit, all members of the committee received a written report containing descriptions of the past activities and projects of all groups. The committee underlines the quality of this document that was well written and presents in an objective way the main strengths and weaknesses of the unit although some information for team-by-team evaluation was somewhat difficult to find.

- The research carried out by the teams led to significant contributions (see team-by-team evaluation below) and they are well known and respected at the national level, although only Daniel Tomé can be considered as a world leader in the field.

- On the whole and on the period considered, the groups have been quite productive since they have published more than 150 original articles either in collaboration or signed as last author by group leaders, as well as review articles. Most of these papers are published in good to very good specialty journals.

#### Assessment of the unit's academic reputation and appeal

- The PNCA laboratory is part of the ALIAS (Aliment, Alimentation et Santé) Laboratory of Excellence and of Paris-Saclay University Idex. It is also involved in the Human Nutrition Research Center d'Île de France (CRNH).

- The director of the unit is renowned in his field of research and is regularly invited to international conferences and has also organized international conferences.

- Team leaders and staff are involved in local, regional, and national collaborations and networks. They are thus strongly connected locally and nationally, but not so much at the international level.

- Team leaders and some staff are members of local scientific and university committees, members of scientific boards of foundations or journals, and regularly contribute to papers or grants reviewing. One strength is the strong involvement in expert panels of ANSES.

#### Assessment of the unit's interaction with the social, economic

- The unit obtained financial support from various companies.

- Several groups are co-inventors of a number of patents some under exploitation, and/or are a driving force behind the creation of small companies and act as scientific advisers for these companies.

- Some themes of research of the three teams put them in an ideal situation to develop translational research.

- A strong link exists with clinicians and interesting translational therapeutic programs are on the right track. However, this link could be reinforced and better defined.

- Members of the unit are willing to share their objectives, projects and results with the general public and have achieved this goal through original events and productions.

#### Assessment of the unit's organisation and life

- All members of the unit recognized the governance as efficient and all members share the scientific objectives of the unit.

- The Laboratory Council meets regularly. Collegial Decisions regarding the life of the unit are being taken collegially.

- Management of the personnel (technicians, students and postdocs) follows adequate rules. Scientific temporary personnel acknowledge the efforts done by the Direction of the unit to follow their career.





- Following the meeting with students and post-docs, it is clear that all PhD students have a very positive opinion about the organization of the unit and teams (adequate repartition of HDR between PhD and day-by-day coaching. They emphasize the leadership of all PIs and the quality of the scientific and human environment. They get financial support to participate to (inter)national meetings and formations (i.e. animal care formation has been paid by the unit for all of them). The common working and lunch places favor the communication between PhDs. The intra- and extra-team exchanges are favored by the monthly letter and the annual doctoral day organized by the Institute. They particularly get advantage of the monthly organization of lab meetings, and would suggest to increase their numbers (twice a month if possible). They also benefit from the network driven by the Head of the unit, and are confident for their future carrier development. They will be happy to actively participate to external collaboration abroad in order to extend their panel of up-to-date expertise and techniques during the thesis period.

- The meeting with technical staff showed that administrative, engineer and technician staffs are highly satisfied concerning the way the unit is governed and the distribution of the activities between staff members. Except for staff in charge of animal housing facility and ANCA chair, others belong to one specific team and their involvements in research projects are clear to them. Engineers and technicians in charge of the animal housing facility and ANCA chair are well integrated in the unit. All personnel are invited to inform the head of unit about internal and external formations of interest and they all mention that their requests are taken into account. Engineers and technicians are all involved in the quality process of the unit towards formal procedures such as metrology for instance but in other aspects an improvement of analytical procedure homogeneity will be beneficial. The only weak point mentioned concerns the information sharing in the unit (top-down and bottom-up); for improving this, they suggest that the frequency of the unit committee increases.

### Assessment of the unit's involvement in training through research

- The unit members contribution to teaching and training is a clear priority of PNCA. This is due at first to the belonging to the Engineers School AgroParisTech. Most of the scientists with academic positions are active in teaching, either organizing courses for Master students or participating in Master teaching at AgroParisTech but also other Paris universities. PNCA participates extensively to the university landscape, and to the training through research of French students from the doctoral school.

- All Master and PhD students are carefully followed during their stay in the lab as well as their activities and careers.

- PhD students are encouraged to present their results in international conferences.

- All students are able to follow specific courses of the different doctoral schools to which the scientists of the unit belong.

- After their PhD's defence, young Doctors are followed by the direction of the unit who knows exactly where they are and in which position, after helping them to find a post-doc, if required.

### Assessment of the five-year plan and strategy

- The scientific strategy is for the most part very good (see team-by-team analysis), based mainly on the continuation of the on-going programme. The combination of emerging ideas and tools as well as collaborations with specialized laboratories for microbiota and bioinformatic analysis are expected to produce new and fruitful results for the next contract, mainly because their feasibility has already been explored.

- The new ideas and directions, at the interface between physiology and nutrition, are especially interesting and may provide novel insights although dispersion must be avoided.

- The forthcoming project seems highly feasible to the committee since it will be run by very good scientists and technicians who have already proved their engagement and dynamism, and because of the availability of most technical tools required to reach the objectives of the proposed project.



## 4 • Team-by-team analysis

**Team 1:** Protein Intake and Intestinal Adaptation

Name of team leader: Mr François BLACHIER

### Workforce

| Team workforce  | Number as at 30/06/2013 | Number as at 01/01/2015 |
|---|-------------------------|-------------------------|
| <b>N1:</b> Permanent professors and similar positions                                   | 4                       | 7                       |
| <b>N2:</b> Permanent EPST or EPIC researchers and similar positions                     | 3                       | 3                       |
| <b>N3:</b> Other permanent staff (without research duties)                              | 1                       | 2                       |
| <b>N4:</b> Other professors (PREM, ECC, etc.)   |                         |                         |
| <b>N5:</b> Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.) | 3                       | 3                       |
| <b>N6:</b> Other contractual staff (without research duties)                            |                         |                         |
| <b>TOTAL N1 to N6</b>   | <b>11</b>               | <b>15</b>               |

| Team workforce  | Number as at 30/06/2013 | Number as at 01/01/2015 |
|---|-------------------------|-------------------------|
| Doctoral students   | 3                       |                         |
| Theses defended   | 7                       |                         |
| Postdoctoral students having spent at least 12 months in the unit | 4                       |                         |
| Number of Research Supervisor Qualifications (HDR) taken          | 1                       |                         |
| Qualified research supervisors (with an HDR) or similar positions | 5                       | 5                       |

## • Detailed assessments

### Assessment of scientific quality and outputs

Originality: studies conducted by team 1 are at the protein/host/microbiota interface with original works on amino acid metabolism in the colon and on its by-products with a special mention about the effect of H2S on the colon. They place team 1 as a significant actor in the field.



Previous works have established the expertise of the team in terms of influence of colonic environment on the functioning of colonocytes and projects are part of a topic of current interest: the influence of changes in protein intake on the intestinal microbiota (composition, activity, metabolites released) and the production of amino acid metabolites which can affect gut mucosa. Of note, investigations on the influence of protein intake on intestinal microbiota appears as a topic recently developed at the end of the 2008-2013 period and seems to rely on expertises largely outside the unit.

Quality: the work of the team leader are for the most part published in journals of good/very good standard (Liu et al 2013 *Inflammatory Bowel Diseases*; Mimoun, et al. 2012 *Antioxid Redox Signal* 17, 1-10; Bouillaud, F., and Blachier, F. 2011 *Antioxid Redox Signal* 15, 379-391) and regularly quoted. However there is no publication in general journals or in journals of high IF.

Quantitatively this production represents about one-third that of the unit. The presentation of the report does not enable to evaluate the quantitative level of publication of each researcher of the team. In addition, more than 20% of the publications by team 1 involved only one researcher of the team. These latter publications of low IF result from a collaboration with China on the study of amino acid transporter expression in developing intestinal cell.

### Assessment of the unit's academic reputation and appeal

If the team does not appear to have been involved in national and international collaborative projects during the 2008-2013 period, it will take part in a recently approved European project in keeping with the team research activities (influence of protein and specific amino acids on the gut and the microbiota).

Two members of this team belong to mainly national but also international scientific expertise authorities.

Involvement in scientific events at a significant international level appears limited outside the contribution of the team leader to the organizing committee of the congress on amino acids, peptides and protein held at Galveston, Texas, US in 2013.

Some international low-key collaborations (China, Chile, Brazil, Spain) have been engaged during the 2008-2013 period, with some researchers, external PhD and postdocs involved temporarily hosted by the team.

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

While several industrial partners are indicated in the unit's report, those involving team 1 are not particularly detailed in the report.

The contribution of the team to the diffusion of scientific culture seems limited.

### Assessment of the unit's involvement in training through research

Outside their statutory obligations, the team members do not have particular involvement in national and international academic programs. Team 1 contributes to the master degree "Aliments Bioproduits Nutrition et santé".

The report mentions that 7 students, working on projects led by team 1, defended their thesis, during the 2008-2013 period. The ratio of PhD student per qualified research supervisor is close to 1 for team 1. The fate of the students is difficult to evaluate on the basis of the information given but all seem to have found a position, permanent for most of them.

Three PhD students are presently working in team 1 as well as several students mainly at Master Level (M1 & M2).

### Assessment of the strategy and the five-year plan

The five year plan of the team, in continuity with the previous period, concerns the impact and consequences of protein intake on the intestine with a recently developed focus on microbiota. Major evolutions compared to the previous period concern a reinforcement of the investigations in humans (clinical study) and particularly on overweight volunteers.

The first part of the project is part of an European project aiming at assessing the influence of quantitative and qualitative variations in protein supply on intestinal microbiota and its metabolism and the consequences on gut mucosa. A clinical study in overweight volunteers will be performed thanks to a large number of collaborations for microbiological/metabolomic/proteomic/fluxomic analysis. The report does not enable to assess whether the team has the



necessary internal expertise for this part of the project. Analysing the large amount of data generated by metabolomic and metagenomic methods is certainly a main issue. Collaboration with the MICALIS institute should be beneficial for the strength of the project and thus reinforced.

The second part of the project is in continuity with the previous work of the team studying the effects of amino acids and their metabolites on epithelial renewal. The new chapter on colon mucosal physiology, opened with the study of H<sub>2</sub>S properties, seems worth to develop and extended to other by-product of microbiota metabolism.

A study project on “the effect of protein-rich diet during gestation and lactation on the risk of later overweightness and diabetes” is mentioned and appears as a thematic dispersion compared to the overall direction of the research activities of team 1. In the same way, the involvement of team 1, through animal models of metabolic stress and inflammation, in the project of team 2 on protein metabolism in catabolic and inflammatory conditions appears dispersive.

## Conclusion

Team 1 is scientifically active with a significant number of publications in journals of good standard with a leader position on the impact of protein and of their metabolites on the gut and microbiota. Researchers of team 1 have however limited degree of international recognition and of involvement in collaborative research projects. At the end of the 2008-2013 period, investigations of the impact of protein intake on microbiota has been intensified and this will be also a guiding line for the next period. This will reinforce the knowledge on the interrelation between protein supply, microbiota, and host intestinal function.

- **Strengths and opportunities:**

Well established expertise in the field of amino acid metabolism in the context of colonic mucosa;

Current interest on the relationship between microbiota and human health.

- **Weaknesses and threats:**

Expertises in omics and microbiology uncertain in order to be able to conduct all the aspects of the project;

Moderate integration in the unit and what is indicate as one of its leading theme: the control of food intake;

Retirement of older researchers expected in the next few years. Will the team still be visible thereafter?

- **Recommendations:**

In terms of project, while the clinical project is ambitious, it seems important to capitalize on the recognized expertise on the action of H<sub>2</sub>S on the gut and by extension of other effectors.

Integration in the projects of processes such as neuroendocrine function of the gut would enable a better interaction with the unit with perspective on the gut-brain axis/microbiota relationship.

External recruitment would enable to acquire the expertise lacking in the team and would ensure long term continuity of the team. The recruitment of an associate professor is indeed a good news, but the speciality, toxicology, could be dispersive. The committee strongly recommend an orientation of the work toward the toxicological aspects of metabolites produced by the microbiota.



## Team 2: Protein Metabolism, Energy Homeostasis and Feeding Behavior

Name of team leader: Ms Claire GAUDICHON

### Workforce

| Team workforce   | Number as at 30/06/2013 | Number as at 01/01/2015 |
|--|-------------------------|-------------------------|
| N1: Permanent professors and similar positions                                   | 4                       | 6                       |
| N2: Permanent EPST or EPIC researchers and similar positions                     | 3                       | 3                       |
| N3: Other permanent staff (without research duties)                              | 1                       | 2                       |
| N4: Other professors (PREM, ECC, etc.)   |                         |                         |
| N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.) | 1                       |                         |
| N6: Other contractual staff (without research duties)                            | 3                       | 2                       |
| <b>TOTAL N1 to N6</b>  | <b>12</b>               | <b>13</b>               |

| Team workforce  | Number as at 30/06/2013 | Number as at 01/01/2015 |
|---|-------------------------|-------------------------|
| Doctoral students   | 4                       |                         |
| Theses defended   | 10                      |                         |
| Postdoctoral students having spent at least 12 months in the unit | 2                       |                         |
| Number of Research Supervisor Qualifications (HDR) taken          | 1                       |                         |
| Qualified research supervisors (with an HDR) or similar positions | 3                       | 5                       |

- Detailed assessments

#### Assessment of scientific quality and outputs

Team 2 encompasses two main research programs, one focused on the cellular mechanisms associated with the metabolism of proteins and the effects of high-protein diet on cellular signalling in peripheral organs (muscle, liver, etc.) and the other related to the effects of proteins and macronutrients on feeding control and associated behaviours (especially rewarding process) under physiological and pathological contexts (metabolic syndrome). These are clearly translational studies associating various patho-physiological conditions in animal models, and the monitoring of signals generated by nutrients in clinical context.



The team has taken risk and made several important contributions, such as establishing the importance of proteins versus fat diets and resistance to obesity using animal models or the relative contributions of dietary proteins to gluconeogenesis in humans. An interesting result is the identification of distinct neuronal pathways activated by sugar or protein in the gut. Furthermore the characterization of protein actions on reward systems opens new perspectives for the study of the metabolic and behavioural cascade events that follow protein ingestion.

Quality: The work of the team are for the most part published in journals of good/very good standard: (Fromentin et al. 2012, 2013 Diabetes, Davidenko et al. 2013 Eur. J. Clin. Nutr, Chevalier t al 2013 IJO, Virtue et al. 2012 Cell Metab, Even et al. 2012 Am J Physiol).

Each topic seems both new and of potential relevance; however, the quality of the output (published papers) should be improved. Publication in key journals will be the only way to convince other groups outside the unit that this work, which has high application potential, should be followed up.

The projects are based on an integrative approach of the effects of macronutrients (and especially proteins) on the peripheral organs (particularly liver) and brain pathways. However, within these topics the team pursues different goals that seem rather scattered. The work on the effect of protein supply in obesity-sensitive rats shows great promise but poorly fits with the future aims of the team, unless the neurophysiological work in the other groups includes the same model. If this is not the case, it is recommended that the team continues this interesting work, but gives the priority to complete the on-going experiments and the publication of the results.

### Assessment of the unit's academic reputation and appeal

None of the scientists of team 2 has received high honours. Some researchers have been invited to few (over 10) conferences (of national level for most of them), which is a rather modest number considering the 5 permanent researchers of the team and which may reflect the fact that not all have reached international visibility.

The team has managed to recruit three new PhD students. Two of them have been selected from the prestigious Agronomy School. In comparison to this excellent attractiveness for PhD students, the team has performed comparatively poorly in terms of attractiveness for post-docs. This is a recognized weakness, partly explained by the difficulties in raising funds from ANR or European contracts. This weakness should be compensated by a more aggressive policy of recruitment of foreign students and post-docs abroad for example by implementing international training programs and participating to European networks.

Obtaining of industrial contracts is generally good, in line with the good technology transfer. Both senior and young investigators have collaborations with European and Chinese labs, although most collaborations are still with French labs. A general policy for a greater opening to foreign labs would reinforce the visibility of team 2 on the international scene.

The group elaborated an effective and fruitful management irrespective of the distinct models of study. This is illustrated by the co-signature of Researchers and Clinical personals of the publications on the most recent articles (Diabetes 2013 (x2), IJO 2013, etc.). This strategy is pertinent. Finally, we recommend that the national (and international) cooperation with groups working on the theme of feeding control and health is maintained and reinforced.

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

This is a strong achievement made by the team during the last period, as testified by the ANCA chair that provided supports for a contract researcher and also allowed production of training materials (video,...) that promote the awareness of food industry.

### Assessment of the strategy and the five-year plan

The research topic of team 2 appears within the current mainstream (see the recent article published in Cell dealing with amino acid sensing and the dopaminergic circuitry in Drosophila brain), with both negative aspects (field with higher competition) but also positive ones (increased visibility). However, the recent activity of the group, involves research in experimental animals (rats, minipigs), which are required to explore intimate mechanisms. This animal basic research would beneficiate from an amplification of humans oriented studies (translational research). Latest publications (2013) in humans in top Journals (AJCN, Diabetes, AJPEM) are consistent with this view.



This would focus the research strategy and counteract the general trend in dispersion of research. More ambitious research is also needed in the future in order to place the topic and the group in a shining place in the map of science. The five year plan of the team, involves a merging of the different trends of the team's research on brain mechanisms related to protein metabolism.

## Conclusion

### ▪ Strengths and opportunities:

Overall, team 2 presents a good scientific production (in quantity) but quality could be greatly improved.

The committee appreciated the good attractiveness for recruitment of young researchers (MC) and dynamic PhD students that bring particular strength in research directions, particularly neuroscience.

The team presents a very good technical expertise in protein metabolism, with a good activity of technology transfer and communication.

The committee appreciated the pleasant working atmosphere.

More generally, the diversity of the expertise of the researchers and clinicians open the way for ambitious transversal projects.

### ▪ Weaknesses and threats:

Lack of scientific focus: though the overall research activity of the team is oriented mostly towards neurobiology of protein intake/metabolism regulation, developed projects and biological issues are extremely diverse ranging from liver and muscle signalling to nutrition disorders. As a consequence, there is a feeling of a lack of strategic vision for the team's general ambition and scientific objectives. It is recommended to overcome this weakness in order to render the team more visible at the international level.

Efficient interactions and complementarities with other teams of the units do not appear as a priority.

Though some clear specific interactions and collaborations between the team and clinical and hospital leaders and professionals could be pointed out, the potential of the team for translational medicine and research may be improved and an active reflection for efficient organization should be considered.

The team suffers from a lack of attractiveness for post-docs, particularly of foreign origin.

A weakness, as the PI also acknowledged, is the low level of national and international academic grants, which will affect the execution of the proposed projects. There is no clear indication how the team will cope with this issue.

### ▪ Recommendations:

For future developments, concepts based on physiological approaches must now be evaluated using targeted pharmacological (DREADD) or genomic (TALENS, CRISPR/Cas9, etc.) approaches. This will be decisive for the group to reach an outstanding status. Indeed, the necessary preliminary characterization of brain networks involved in protein signalling molecules, and the setting up of functional tests using "transgenic" rats should now be actively exploited to the study of protein intake-driven plasticity of feeding behaviour. If the lack of resources and facilities prevents expensive or highly technical works being done at the UMR, these crucial experiments could be done in collaboration with other labs, for instance at the national level through the Alias Labex or the Saclay IDEX or through the H2020 European programme. The committee encourage also a more ambitious publication policy and application to international grants.



### Team 3: Protein, Amino Acids Metabolism and Metabolic Syndrome Prevention

Name of team leader: Ms Dominique HERMIER

#### Workforce

| Team workforce   | Number as at 30/06/2013 | Number as at 01/01/2015 |
|--|-------------------------|-------------------------|
| N1: Permanent professors and similar positions                                   | 2                       | 2                       |
| N2: Permanent EPST or EPIC researchers and similar positions                     | 3                       | 3                       |
| N3: Other permanent staff (without research duties)                              | 1                       | 1                       |
| N4: Other professors (PREM, ECC, etc.)   |                         |                         |
| N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.) |                         | 1                       |
| N6: Other contractual staff (without research duties)                            | 1                       | 2                       |
| <b>TOTAL N1 to N6</b>  | <b>7</b>                | <b>9</b>                |

| Team workforce  | Number as at 30/06/2013 | Number as at 01/01/2015 |
|---|-------------------------|-------------------------|
| Doctoral students   | 3                       |                         |
| Theses defended   | 5                       |                         |
| Postdoctoral students having spent at least 12 months in the unit |                         |                         |
| Number of Research Supervisor Qualifications (HDR) taken          | 1                       |                         |
| Qualified research supervisors (with an HDR) or similar positions | 4                       | 5                       |

#### • Detailed assessments

##### Assessment of scientific quality and outputs

Team 3 investigates the relationship between protein and amino acid intakes and the development of metabolic syndrome (MS). This is an important and original field of research in nutrition and health. Only few research groups around Europe focus on this topic.

This is obviously one of the strengths of the unit, in term of potential and originality.

Two relevant aspects are more particularly investigated:

1) the alterations in protein metabolism (protein synthesis/proteolysis) in general, and more specifically the alterations of arginine and NO metabolism, at MS onset;





2) the impact on MS development of changes in protein intake (qualitative as well as quantitative) (such as an increase of in sulphur amino acid intake), or of changes in protein metabolism by the  $\omega$ 3 fatty acid intake.

The design of most of the studies is based on the use of rodent models of MS, which are relevant. The questions addressed, mostly concern the links between protein metabolism and adiposity, low-grade inflammation, oxidative stress, endothelial dysfunction or insulin resistance.

The use of stable isotopes as metabolic tracer is an important tool in order to fully investigate human physiology.

Intervention studies in human will validate mathematical models of protein metabolism. This has been so far only partly achieved.

The long-term aim is to validate strategies for nutritional interventions in humans.

The number of publication in the 2007-2013 period is not exceptional: about 25 research papers with PI as first or last author for 4 full time-equivalent researchers (almost 1 paper/year/member). Some members of the team are clearly more active in term of publications and communications.

One out of the 3 “notable achievement” of the unit is issued from works of team 3. The paper, published in Am J Clin Nutr, demonstrates, through the use of new metabolic tracer method in humans and compartmental modelling of the metabolic system, that the synthesis of NO from dietary arginine is linked, not only to the systemic availability of the amino acid, but rather relates to its metabolic compartmentalization. Other papers are of good to very good level in specialized journal of the field: Camilleri et al 2013 J Nutr; Poupin et al. 2011 AM J Physio; Verger et al 2012 PloS One.

Tracer methods has also been used to experimentally evaluate the consequences of high fat/ high sugar diet on pathways involved in protein and amino acid metabolisms in different tissues (intestine, liver, heart...). The published (or submitted) papers, based on experimental studies in animals, reveal that under conditions of “malnutrition” (high fat/high sugar diets), protein intake is still able to reduce lipogenesis and lipid accumulation in the adipose tissue.

The analysis of the publication list also reveals, through the co-authorship, the collaborative potential of the members of the team with other groups.

There is a clear focus on local communication, but communication at international level is less developed.

The inter-disciplinarity is not really obvious. However, the members of the team share several expertises that are complementary. Competences in both animal experimentation, and human intervention studies approaches can be considered as a positive point, if common questions are taken into consideration. The use of stable isotopes to trace body metabolism is a plus versus the cellular and molecular analysis, in order to develop an integrative physiology approach.

### Assessment of the unit's academic reputation and appeal

There is only limited involvement of team 3 in international consortia and projects, whereas the head of the unit and other members are clearly involved in international consortia and networks. This could be helpful for team 3 in order to extent its output at the international level.

Collaborations with foreign laboratories (Riddet Institute New Zealand, DIFE and Hannover medical school in Germany and Texas Tech University).

There is not reporting of invitation of the members in international meetings.

It is difficult to evaluate the link of the members of team 3 with industry and non-profit association, since the report does not mention the name of the contact persons. Some future actions with industries (linseed oil industry, other “confidential” industries) are mentioned.

Strong involvement in expert committee (Nutrition at ANSES).

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

This is a very visible part of team 3 activity.

Members have produced 3 ANSES expert reports during the evaluation period,

Members participated to 3 training sessions targeting professionals.



### Assessment of the unit's organisation and life

Team 3 has developed expertises (both in animal studies and human intervention studies), and collaborations, that are adequate in view of their objectives. However, the interactions with the other teams within the unit cannot be easily visible. The expertises and models developed should be shared with the other members of the unit.

### Assessment of the unit's involvement in training through research

Team 3, despite its low critical size, had a high potential for research training, since 4 members are holding an HDR, which represents 40 % of the HDR of the unit.

Five PhD theses have been defended with success during the period of evaluation, with several publications issued from the experimental work. (N POUPIN, 2013; A-S FOUCAULT, 2012; N GUELZIM, 2011; J MAGNÉ, 2009; M VICTORIANO, 2009). Two PhD are currently going on, with themes clearly oriented towards human nutrition.

### Assessment of the strategy and the five-year plan

On-site visit was helpful to evaluate team 3 project.

Work will be pursued

- to analyze the paradoxical impacts of protein and amino acids on insulin signaling and on the risk of being overweight and developing MS.

- to evaluate the natural isotopic signatures of metabolic deregulations during the initiation of MS.

- to explore the mechanisms involved in postprandial low-grade systemic inflammation (in different organs and on vascular endothelium) and the impact of dietary protein quality on preventing this inflammation.

- to evaluate the effects of the consumption of cysteine- and arginine-rich vegetable protein sources on cardio-metabolic risk markers and factors. Preliminary studies in animals have suggested that the consumption of these proteins (which promotes glutathione and nitric oxide synthesis) limits the development of physiological or high-fat high-sugar diet-induced metabolic dysfunctions. The aim is to confirm these observations in humans.

- to analyze the Influence of dietary n-3 fatty acids on protein metabolism and the implications in terms of initiation factors of MS.

The team will also contribute, through the determination of markers for protein consumption, to the work of team 2. The project is in direct line with the research activities developed upon that last five year, and it is quite interesting to see more links with the objectives and approaches of the two other teams.

### Conclusion

- Strengths and opportunities:

- Relevance of team 3 orientations to public health.

- Some interactions with team 2 also this could be reinforced.

- Efforts to expertise transfer (expertise recognized by ANSES).

- Recognized expertise at least at the national level, in the field of integrative physiology (metabolic fluxes evaluated with stable isotopes in vivo, rodent models, human physiology, compartmental modelling of protein metabolism).

- Weaknesses and threats:

The size of the team 3 is modest, but there is a potential of expertise, which can profit to the scientific activities of the whole unit. The scientific communication at the international level remains quite low during this period, and compared to the other teams.

International recognition of the work done remains questionable;

Few postdocs in the team;



The scientific strategies are too often still descriptive.

- Recommendations:

As for the whole unit, an increase publication effort (number, level) should be done;

In the same way, emphasis on the development of mechanistic orientations has to be given;

Recruit postdocs;

Within the coming period, put in place the conditions for a new leader to emerge within the group or be recruited from outside.



## 5 • Conduct of the visit

### Visit date:

Start: February 4<sup>th</sup> 2014 at 09.00 am

End: February 4<sup>th</sup> 2014 at 05.00 pm

Visit site: AgroParisTech

Institution: INRA

Address: 16 rue Claude Bernard, 75005 Paris

### Conduct or programme of visit:

|                 |  |
|-----------------|--|
| 08.30-09.00 am: | Greeting of participants:  |
| 09.00-09.30 am  | Meeting of the experts committee in presence of the AERES scientifique delagate (DS)                                     |
| 09.30-09.45 am  | Meeting of the experts committee with the unit director in presence of the DS  |
| 09.45-12.30 am: | Presentation in presence of the staff unit:  |
| 09.45-10.00 am  | General presentation by the unit director  |
| 10.00-10.50 am  | Presentation and discussion team 1: Mr François BLACHIER   |
| 10.50-11.40 am  | Présentation and discussion team 2: Ms Claire GAUDICHON  |
| 11.40-12.30 am  | Presentation and discussion team 3: Ms Dominique HERMIER   |
| 12.30-01.00 pm  | Meeting with the INRA, AgroPARisTech representatives   |
| 01.00-02.00 pm: | Lunch  |
| 02.00-02.30 pm: | Parallel meetings with :<br>- researchers and clinicianans<br>- PhD students and post-doc<br>- ingeneers and technicians |
| 02.30-02.45 pm: | Meeting with the research director   |
| 02.45-05.00 pm  | General discussion restricted to members of the experts committee  |



## 6 • Supervising bodies general comments

**UMR Physiologie de la nutrition et du comportement alimentaire (PNCA)**  
AgroParisTech-Inra

*Réf.: Rapport d'évaluation AERES - S2PUR150007829 - Physiologie de la nutrition et du comportement alimentaire - 0753465J*

### **General comments**

The direction and the members of the Research unit agree with the comments of the AERES Expert Committee on the scientific positioning, outcomes and projects of the research unit. They also agree with the recommendations and advices made by the Committee and will take them into account in order to improve the research and the positioning of the group.

Among recommendations and advices, some seems particularly important and will be subjected to a particular attention. The strengthening of mechanistic approaches will be performed by internal development, by training of the members of the unit, by national and international collaborations and by trying to attract more efficiently researchers and post-doc with the appropriate complementary expertise's. An effort will be made to more efficiently coordinate the research activities between the team by improving the internal collaborations, more particularly on the modulatory effect on protein and amino acid on homeostatic control of energy balance and the risk of metabolic dysfunctions associated to metabolic syndrome. In addition, due to the progressive retirement of part of the seniors of the unit, allowing new leader to emerge within the unit and attracting researcher from outside will be an important challenge for the direction in the next coming years.

For the different teams:

Team 1 will continue to focus on the protein and amino acid-derived metabolites produced by the microbiota and on their potential effects on the host by developing more mechanistic approaches. The team will particularly strengthen his expertise in omics approaches and meta-data analysis, through different collaboration (INRA platforms, ALIAS network, European project MyNewGut, other international collaborations) and by promoting the individual training on these approaches of the different members of the team. This will also allow to provide original results on the potential role of the microbiota on physiological functions and health and to further improve the visibility and the level of the publications of the team.

Team 2 will concentrate his activity on the mechanisms by which peripheral protein and energy metabolic events modulate energy nutrient (glucose, fat) pathways and produce signals that modulate the activity of brain area involved in the homeostatic and non-homeostatic control of feeding. The team will strengthen his expertise related to mechanistic molecular analysis, omics and imaging techniques using the original animal models developed by the team and by also using knockout animals through collaborations with

national and international groups. These developments associated to the recognized expertise of the team on integrative physiology (phenotyping, feeding behavior, stable isotope studies, gene expression, cell signaling) in animal and humans will participate to further increase the quality of the publications and the international visibility of the team.

Team 3 will mainly focus on the exploration of the mechanisms involved in the impact of specific amino acids (cysteine, arginine) and their interaction with omega 3 fatty acids on the initiation of metabolic syndrome and associated risk factors including low grade inflammation. The team will also try to strengthen his activity on more mechanistic approaches in addition to his recognized expertise in integrative physiology (stable isotopes, compartmental modelling of protein metabolism, rodent and human studies). This will be performed in association with the overall effort on the research unit on this direction and also through national and international collaborative interactions and activities for the use of molecular and omics techniques that should participate to improve the visibility of the team.

A handwritten signature in black ink, appearing to read 'Daniel Tomé', with a long horizontal stroke extending to the right.

Daniel Tomé  
PNCA Director  
With the agreement with the supervising institutions