

Écologie et physiologie du système digestif

Rapport Hcéres

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

Section des Unités de recherche

Evaluation Report

Research unit :

Ecologie et physiologie du système digestif (UEPSD)

From INRA



March 2009



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et de l'enseignement supérieur

Section des Unités de recherche

Evaluation Report

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Ecologie et physiologie du système digestif (UEPSD)

From INRA

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

March 2009



Evaluation Report



The research unit:

Name of the research unit : Unité d' Ecologie et Physiologie du Système Digestif (UEPSD)

Requested label: Unité propre INRA

N° in case of renewal : 910

Head of the research unit : M. Gérard CORTIER (past director) ; M. Joël DORE (new director)

Main research organization:

INRA

Other institutions and research organization:

Date(s) of the visit :

2nd-3rd February 2009



Members of the visiting committee

Chairman of the committee :

Mrs Arlette DARFEUILLE-MICHAUD, Université Clermont 1

Other committee members :

Mrs Christine CHERBUT, Nestlé Research Center, Lausanne, Suisse

M. Jean-Frédéric COLOMBEL, CHRU, Lille

Mrs Claudine MEDIGUE, Génoscope, Evry

M. Bruno POT, Institut Pasteur, Lille

M. John WALLACE, Rowett Research Institute, Aberdeen, UK

CNU, CoNRS, CSS INSERM, INRA, INRIA, IRD.....representatives :

M. Michel RIGOLET, CSS INRA

Observers

AERES scientific representative:

M. Philippe NORMAND

University or school representative:

M. Patrick ETIEVANT, Head of Department AlimH of INRA

Research organization representative (s) :

Mrs Emmanuelle MAGUIN, Head of Department Mica of INRA



Evaluation Report

1 • Short presentation of the research unit

The unit comprises three teams with a total number of 13 INRA researchers (4DR, 9 CR), 8 engineers (4IR, 4IE), 15 technicians and 4 administrative assistants who are all INRA personnel, and between 7 to 10 PhD students and 5 to 7 post-docs. Seven scientists hold a habilitation to lead research (HDR), of which one was defended during the present 4-year contract. Thirteen theses have been defended during the same period. The number of active scientists (publishing or “publiants”) is 13 out of 13 permanent scientists.

2 • Preparation and execution of the visit

The visit had been carefully prepared and members of the committee had received pdf files of the scientific report in good time, as well as printed documents for the members of the committee who requested them. Globally, the written document was well constructed, although sometimes difficult to analyse because of redundancies between the Unit teams.

Given the composition of the committee, and in response to a demand from AERES, part of the interview sessions was conducted in English. Very efficient practical organisation provided excellent conditions for the visiting committee to analyze the scientific work done by the unit.

During the visit, the scientific quality of the oral presentations was excellent and the international members were presented clearly the information essential to understanding the various projects and the operation of the unit and its component teams. The dialogue between the director and co-directors of the unit and the members of the committee was greatly appreciated by the committee. The whole unit took part in the debates, except of course the interviews with the different staff categories. The interviews with the different staff categories had been well prepared, enabling the panel to evaluate the general atmosphere within the unit as well as individual teams. The panel was impressed by the enthusiasm of the team members.

The committee was provided in advance with a report detailing the scientific activities of the unit during the period 2004-2008, and how the unit will operate in the framework of the very large unit (TGU) Micalis. The visit took place over two days, during which work of the unit and of its constituent teams was presented orally, with separate discussions taking place with technicians, students and scientists as well as the management team. A meeting also occurred with the governing institutions, INRA (Dpt AlimH et Mica), which enabled more precise description of the strategies of the unit as well as the evolution of its role according to the different points listed in the mission letter. The interviews with the governing institutions clarified the position of the unit in the strategic scheme of the two departments.

An interview with the unit head and the two deputy-directors at the end of the visit enabled clarification of a few points, in particular concerning the flow chart and the modifications in the unit structure that will result from its integration in the TGU Micalis.



3 • Overall appreciation of the activity of the research unit, of its links with local, national and international partners

The unit UEPSD (Unité Ecologie et Physiologie du Système Digestif) is an INRA unit with the Department Human Nutrition (AlimH) as pilot and the Microbiology Department and the food chain (Mica) as secondary department. The unit is situated on the INRA site of Jouy-en-Josas in two neighbouring buildings, one of which dates back to the construction of the site in 1946 while the other one is very recent.

The general theme of research done in the Unit concerns the description of the gut microbiota and its links with human health. The Unit's primary aim is to help define how nutrition can prevent several of the main pathologies affecting man, by improving our knowledge of diet-microbe-host interactions and their impact on intestinal microbial ecology and digestive functions. This unit is well recognized internationally, as testified by the many invited lectures (Europe, United States, Australia) and the impressive number of publications in international peer-reviewed journals. Some members of the unit have succeeded in publishing their results in very good journals in their field, including Gut, NAR, J. Immunol., JBC, J Am. Chem. Soc., AEM, and Environ. Microbiol. One recent paper was published in the generalist journal, PNAS. The average number of publications of the unit per year is 3 per researcher and per year; this rate is relatively constant over the reference period (2004-2008).

Many members of the Unit are involved in teaching duties (approximately 130 h per year) at various levels, L2 (ENSBANA Dijon), L3 (La Roche-sur-Yon, Grenoble), M1 (IESIEL Rennes, Paris 11, Paris 6, INAPG, Versailles-Saint Quentin), M2 (Chatenay-Malabry, Paris6), Institut Pasteur. They also participate in international education programmes (European Labhealth, Roadshow).

4 • Specific appreciation team by team and/or project by project

Team 1 « Biodiversité phylogénétique et métagénomique fonctionnelle du microbiote intestinal humain »

This team has published an impressive number of papers (53 ACL) in good journals (mean impact factors: 2,49 in 2004, 3,42 in 2005, 3,79 in 2006, 3,83 in 2007, 4,53 In 2008). With increased emphasis on disease, the impact factor of the journals has been increasing, with a recent paper in PNAS providing a high impact for the group. The collaborative links that have been forged with leading foreign groups in metagenomic projects should ensure that some future papers appear in the highest-IF journals. In terms of invitations to deliver plenary lectures, the team leader has a first class record (18 conferences), and 3 conferences were undertaken by others in the team.

The work of this team is of a fundamental nature, the results of which will underpin future socio-economic development. The team should be aware of the potential of their observations, as we believe they are, but should not be pressed unduly for immediate applications of their research. In other words, they need to focus on their strengths.

It is hard to foresee transfer of operational knowledge to industrial users in the immediate future. The team has extensive international partnerships but is still involved primarily in the production of knowledge.

The quality of the work done during the last four years has been excellent. The work on phylogenetic analysis of the human intestinal microflora is at the top of world ranking. The concept of moving from phylogenetics to metagenomics sounds wonderful, and is entirely appropriate given our present understanding of human gut microbial ecology, but it is risky. It is intended that the research will result in global analysis of gut function, something that has yet to be proved. Team 1 must guard against a more opportunistic approach. The exception would be where links with the other groups are involved. For example, bacterial production of anti-



inflammatory factors/signals should be investigated from the metagenomic perspective, but also from the genetic one with *F. prausnitzii* - their proven anti-inflammatory species. The link between obesity and the gut microbiota also carries some doubt on whether it is a cause or an effect, but the risk is worth taking given the health implications in an obesogenic world.

The team has good vision of the status of their scientific subject and also of the latest techniques available for their investigations. There is concern, however, about how much of the technical activity - sequencing, metaproteomic, metabolomic, etc. - is not an integral part of the team's own technical capability. In this context, bioinformatics needs to become part of the team's core strength rather than a sub-contracted activity. Especially, to efficiently explore the functions of the human gut microbiote, resources (databases and tools) allowing to bring together the data produced by nutritional studies are really missing today. Micalis may change the scientific landscape, offering opportunities for collaboration and scientific/technical development.

- Strengths

The principal strength of the team resides in its leader. Its other strengths include (a) its excellent networking throughout Europe and with the US, (b) complementarity with the other teams, resulting in excellent synergy between the teams, (c) emerging good connections with clinical teams, (d) it is well equipped, with good equipment (second arm of robot coming), and (e) high international recognition for its achievements.

- Weaknesses

The reliance of the team on its leader is too heavy, particularly with his promotion as head of one of the Micalis axes. A natural successor is not evident, so there is concern about how the leading role of the team can be sustained if the present leader can devote only a fraction of his time to the team. Interactions with clinicians should be more regular, less sporadic. The metagenomic approach to describing overall gut function may prove to be too difficult, or even not valid. The team already studies the metagenome and the metaproteome. Whether extending its interest, as suggested, to a metatranscriptome approach needs careful assessment. Certainly, the metagenomic screening should be reconsidered in line with the unit as a whole. Investigation of xylanolytic and mucinolytic activities is less important, in the whole picture of the unit, than studies of antiinflammatory properties.

The team should always consider, before submitting data for publication, the value of their intellectual property for patent protection.

- Recommendations

Personnel changes need to be investigated to compensate for the partial loss of the present leader due to the creation of the Very Large Scientific Unit (TGU). If the more junior members of the team are not ready, recruitment of a more senior scientist must be considered.

In addition to the above, bioinformatics must become a core activity of the team, either by training or recruitment.

Focus on the metagenome and properties should be on topics most relevant to the unit's overall remit. Metatranscriptomics should be delayed until metagenomic approaches are mastered, possibly pursuing new partners with that interest.

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A+	A+	A	A



Team 2 « Interactions des bactéries commensales et probiotiques avec l'hôte »

The scientific productivity of Team 2 of the UEPSD is quite impressive. In total, the team published 65 ACL for the period of October 2004 to November 2008, with mean impact factors of 4,26 in 2004, 3,30 in 2005, 3,75 in 2006, 3,72 in 2007, and 3,58 in 2008, 7 reviews and addressed 5 conferences as invited speaker. For a team of this size this is a very good average, which is mainly due to close links and fruitful collaboration with clinicians and to access to a considerable number of students (The European LabHealth initiative).

Although an MD is no longer physically active in the team, there are very good prospects for future clinical relevance given recent developments, including the possibilities offered by the discovery of a potential new anti-inflammatory compound from *Faecalibacterium prausnitzii*, the RNA silencing experiments and the DNA delivery approach by *Lactococcus lactis*.

A complex scientific network has been developed over the years, mainly with INRA laboratories locally and throughout France. In addition, a number of international collaborations, in Europe and the US, have been set up. Although this network is very useful and enriching, it creates an inherent risk for diversification in research topics, loss of focus, reduced quality in each individual topic and therefore dilution of output. Having access to a substantial scientific network is helpful in fundraising, since multi-partner projects can more easily be applied for (e.g. EU projects).

Collaborative links have also been built with the industry. Although limited in number, these contracts have provided financial benefit to the team. The yield in terms of innovation and knowledge has perhaps been more limited, but successful collaboration with the industry has added to the reputation of the laboratory. Contracts have been set up with several different industrial partners, avoiding the pitfall of 'being the lab of' industry X, Y or Z. A particular initiative to mention in this context is the creation of a French Probiotic Network that assembles the French probiotic industry and the French research labs active in that field on a yearly basis in order to discuss new developments and to exchange ideas for future research projects / collaborations.

The team leader, in close connection with the director of UEPSD, has been quite active in communication towards the public, via websites, newspaper articles and other local initiatives. In a field of research such as probiotics, which requires continuous communication and fine-tuning of the information dispersed by third parties on the Internet or by any other means it is extremely important that specialists in the field can give a scientific and balanced judgment on the topic and answer questions from the public.

The type of research performed has strong potential for practical application, especially since the projects have clear clinical importance. The possible use of these applications in an agricultural or food environment, however, will probably be much more restricted, partly because of the rather negative view of genetically modified organisms by the European population. Still we believe the potential for socio-economic benefit is very high, notably in the medical field. We can see good prospects for some of the applications that are currently being optimized. Care should be taken not to publish results too quickly and to consider a prospective investigation of the potential patentability of the new findings at an early stage (*F. prausnitzii*).

As mentioned before, some of the topics are quite new and original. This clearly adds positively to the general appreciation and quality of the Team. The drawback is that this type of research has an inherently higher level of risk. The elevated risk can probably be reduced by increased manpower and improved focus on a few of these high-risk topics. The choice for future high risk topics will need to be made in accordance with recommendations from MICALIS, and this risk will need to be matched with some other counterbalancing research activities in the MICALIS setting.

Due to the large amount of themes covered by this Team, there is a strong probability some will turn out to be successful. Careful monitoring will be necessary to choose which research axis will be most successful.

The panel perceived a need to avoid a further diversification of the projects. The team might even gain in efficacy and quality by focusing on the most promising subjects; we feel there will soon be a need for a re-assessment of priorities and topics chosen in respect of the requirements from MICALIS. Also the research themes of the other teams should inform the decision making process. At the same time, it is recognized that this type of research is highly multidisciplinary, involving microbiology, immunology, molecular biology, and requires experiences in cellular and systemic biology as well as in animal model development. The existing links



within UEP are therefore very useful in this respect and should preferably be maintained or even strengthened in the framework of the MICALIS project.

The proposed re-assessment of the research themes will possibly allow a more directed and therefore more efficient use of the financial resources available. There is no real restriction imposed by the present budget, but the size of the Team and the number of research projects is large enough to cause concern that, if there is a period of less successful project applications, the Team might face certain shortages. A reduction of the total number of projects and focusing more on the core activities will minimize this risk.

- Strengths

This Team has many strengths. First, there is the team leader, who is very enthusiastic, dynamic and successful in motivating young people. He is readily available for proper guidance, as was obvious from students and technicians comments.

Also, Team 2 has strong relations with the two other teams within UEP and with clinicians. This creates a critical mass that is necessary for the type of multidisciplinary research.

The research themes in DNA delivery and in anti-inflammatory activities are very promising axes with a high potential for therapeutic implementation of the results. It seems to us that the research activities are in line with the research priorities of INRA.

- Weaknesses

As mentioned before, we are concerned that Team 2 currently deals with too many topics. This might dilute the efficacy of the research and raise some questions on competitiveness of the Team on all these axes. The necessary exercise to decide on the axes having high priority will be difficult but probably needs to be made bearing in mind the MICALIS project priorities and the lateral activities of the other two Teams of UEP in this future setting. From this point of view a formal strengthening of the immunology side might be desirable.

The medical axis for obvious reasons has gained considerable attention at the expense of research on the food axis.

- Recommendations

A formal strengthening of immunology aspect is needed in this team. A position for a researcher in immunology should be opened.

Maintaining the existing links with other teams of UEP is needed to achieve goals in such multidisciplinary projects, involving microbiology, immunology, molecular biology, and requiring experience in cellular and systemic biology as well as in animal model development.

Departmental recommendations might require a re-activation of the food axis.

In an attempt to reduce the number of current research activities, considered should be given to transferring some of the current applications to a start-up company, which can be embedded in the tissue of the current laboratory, but which would have independent financing and a dedicated staff, and would bear the technology-transfer risks in an independent way.

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A	A+	A	A



Team 3 « Fonctions métaboliques du microbiote intestinal humain »

Considering the small size of this team (2 INRA researchers, 2 engineers and 2 technicians), the scientific productivity is good: 29 articles in peer reviewed journals of average or good quality (mean impact factors: 1.74 in 2004, 3.73 in 2005, 3.40 in 2006, 2.98 in 2007 and 2.75 in 2008). In addition, the team is actively seeking external funding.

The team has forged many collaborations with research units within INRA (MICA, BIOBAC and UBLO) and outside INRA (INSERM units). There have been recent improvements in the number and quality of financial contracts with industrial partners (Nestlé). The team's projects cleverly used the strength of their gnotobiotic animal facility to develop their programme. One of the researchers is strongly involved in managing and in the development of this platform. This is sometimes an advantage for the practice of experimental procedures but this can decrease the effective involvement in innovative scientific programs.

The type of research performed is likely to have a strong potential for practical application, especially since a number of research directions have clear clinical importance. New projects are highly promising, with recent studies showing the importance of the gut microbiota in obesity and in associated pathologies like Non-Alcoholic Fatty Liver Disease (NAFLD) or Non-Alcoholic Steato-Hepatitis (NASH). The proposed NASH programme will provide useful knowledge if well conducted. Another new project will target the gut microbiota-brain axis, investigating whether the pathogenesis of autism, for example, could be related to abnormal gut microbiota and to microbial production of toxic metabolites (for example, oxidized indole derivatives). This new project should develop successfully, given the advantage of the globally exceptional animal facility.

Some aspects of the projects are very risky, but they are extremely promising, and success in any of them would have immediate and very high impact.

The main problem remains the small size of this team compared to the ambition of the two major programmes. Of course, the research purposes offer very interesting perspectives. However, it will be necessary to establish links and priorities between the various projects, since all of them are highly competitive.

To be successful, these projects will require additional manpower as well as tight collaborations with the two other teams. As the new team leader is relatively young, management support from the unit might be necessary to help with these new demands. The proposed decrease in time spent on research by the former leader will also make progress on the brain-related project more difficult.

The missions of the AlimH INRA department are to help define nutrition strategies for preventing some important diseases in humans and to improve knowledge of diet-microbe-host interactions. The Team 3 projects are highly consistent with the AlimH main goals, therefore, particularly in host-microbes crosstalk.

The quality and the complementary knowledge of the teams in this unit, the unique platform of the animal facility, and the strong relationship with clinicians belonging to INSERM offer significant safeguards for success.

- Strengths

The team should be supported because of the importance of the research field and its potential direct implications in human health. In addition, the projects of this team are consistent with the recommended themes of the AlimH INRA department and this Team is complementarily in its skills with the rest of the unit.

The young leader in charge of the team is dynamic. He is readily available for proper guidance, as was obvious from PhD student and technician comments. One of team's researchers is strongly involved in the functioning and development of the animal facility platform.

Some aspects of the projects are very risky but are extremely promising and success would have a very high impact and a strong potential for technology development.

- Weaknesses

Some aspects of the projects are very risky, but we believe that the possible benefits outweigh the risks.

The panel has concerns that Team 3 will be too small to achieve the planned projects and stay internationally competitive, especially with the involvement at 80% of one of the researcher in the functioning of the animal facility.



- Recommendations

The main recommendation for the success of the proposed projects is to reinforce the team and to add complementary competences.

This team needs also to continue to develop organic relationships with the other two teams of the unit.

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	B	B	A

5 • Appreciation of resources and of the life of the research unit

– In terms of management :

- Management is done in a transparent way at the unit level, to the point of view of the director and co-directors. This is not really the feeling of all the researchers of the unit.
- Good financial management.
- Excellent access to common services.
- Average quality process.

– In terms of human resources :

- Adequacy of competences of the team to the project :
 - There is a need for 3 positions : one in bioinformatics (Team 1) and one in immunology (Team 2), one with complementary competences for Team 3. Support to help the leader of team 1 is also needed.
 - The relationship with clinicians needs to be strengthened.
- Prospective vision, permanent formation and planned hiring :
 - Excellent, hard to plan but needs to be done in the context of new initiatives within the TGU Micalis.
- Excellent integration of PhD students.
- No problem concerning hygiene and security.

– In terms of communication :

- Good policy of communication.
- Very good scientific animation.



6 • Recommendations and advice

— Strong points :

- Uniqueness of topic.
- International recognition.
- Strong team leaders.
- Good spirit in the unit.
- Access to high quality platforms.

— Weak points :

- Communication between members of different teams.
- Absence of technology transfer through patents or databases.
- Prioritize the dialogue “immunity and food” (department recommendation).
- The panel underscored that the citation of the publications is high. However, the production has potential to be improved by increasing the number of publications in very high impact journals.

— Recommendations :

- Departmental recommendations might require a re-activation of the Food axis.
- More day-to-day interactions with clinicians should lead to publication of results in very high impact factor journals.
- Need for focussing on topics. In an attempt to reduce some of the current research activities, some current applications might be transferred to a start-up company, which can be embedded in the tissue of the current unit, but which would have independent financing and a dedicated staff, and would bear the technological risks in an independent way.
- Need for prioritization of recruitment. A recruitment problem was also noted, with a clear question to try and preserve present knowledge and competences. More specifically the “poste d’ assistant-ingénieur”, dealing with the culture collection and the cultivation of fastidious microorganisms seems to be identified as highly priority. The formal nomination of a dedicated person for this task seems desirable.

More general recommendations :

- Following discussions with the staff, it was noted that the dialogue between the different Teams of the UEPSD may need to be prioritized. This could be achieved by creating more opportunities for daily, informal meeting (e.g. around a common coffee table).



- An increasing problem of space was noted. This might be a temporary situation, as probably the new MICALIS building should bring a solution to this problem.

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A+	A	A	A



Monsieur Gérard Corthier

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Answer to AERES evaluation of UEPSD

Jouy-en-Josas, the first of April 2009

Dear Sir,

I have received the AERES evaluation of my Research Unit INRA U910. We discussed the document with the team leaders and our comments are as follows: We appreciate that the Committee enjoyed the visit and the documents that we have written. We also did find the visit and the discussions very interesting and constructive. It was a challenge to ensure that we would convince the experts panel our past research and our projects were good. We accepted it and we did the best we could (documents and oral communication) to achieve this challenge.

According to the AERES report it seems that we succeeded since we do not find any major negative remarks on the 4-years evaluated period. Reading the document, we feel that our projects were regarded as challenging and of high quality by the Committee and we certainly appreciate.

In the AERES document, there are some interesting suggestions for the future concerning strengths and weaknesses of our teams. There is nothing which implies a re-writing of any part of the project. We do accept the comments as good advices which will need to be discussed with our INRA leaders and put into the context of MICALIS. Since our Research Unit will be fused in January 2010 in a larger one (350 persons instead of 80), two INRA Departments are concerned by our research projects. The Committee suggested the recruitment of several new permanent positions to build on the strengths of our teams (about 4 new persons). We greatly hope that our INRA leaders will be able to follow these recommendations.

We have no particular comments to add to what we consider as a positive AERES report

Sincerely

G. Corthier