Infection à hélicobacter, inflammation et cancer

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Infection à Helicobacter, inflammation et cancer

INSERM U853

From the

Université Victor Segalen Bordeaux 2

INSERM

Mai 2010

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Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

Mai 2010

Research Unit

Name of the research unit : Infection à Helicobacter, inflammation et cancer

Requested label :

N° in the case of renewal : INSERM U853

Name of the director : M. Francis MEGRAUD

Members of the review committee

Chairperson :

M. Philippe GLASER, Pasteur Institute, Paris

Other committee members :

M. Vladimir PELICIC, Imperial College of London, UK

M. Ivo GOMPERTS BONECA, Pasteur Institute, Paris

M. Richard DUCATELLE, University of Gent, Belgium

Ms Evelyne COUDRIER, Curie Institute, Paris

M. Rainer HAAS, Ludwig Maximilians University, Munich, Germany

Ms Dominique LAMARQUE, University of Franche-Comté, Besançon

Committee members nomminated by staff evaluation committees (CNU, CoNRS, INSERM and INRA CSS….):

M. Michel SIMONET (CSS INSERM)

Observers

AERES scientific advisor :

Ms Claire Poyart

University or School representatives :

M. Alain BLANCHARD (University Bordeaux 2)

Research Organization representatives :

Ms Christine TUFFEREAU (INSERM)

1 • Introduction

- Date and execution of the visit:

The visit took place on the 10th of December 2009. The laboratory director made a general presentation of the team's main achievements and its activities and clinical networks. The four major research topics and an additional project were presented in the morning together with discussion of the research project. The committee met with representatives from Bordeaux I University, IFR, UFR, and INSERM which all showed strong support of the activities of the team. During the afternoon, the committee visited the laboratories and discussed with students and postdocs in front of 7 posters. The committee then heard separately the students and post-docs, the scientists, and the technical staff The visit was concluded by a 2 closed-door meeting of the committee to prepare the present report.

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

The laboratory was initially setup by F. Mégraud in 1996. It became an INSERM unit (E113) in 2000, (U920). It averages a total of 20 people and is localized on the University of Bordeaux 2 campus. The laboratory is working on Helicobacter infections and, in the recent years, has setup several new tools for identifying and studying new genes involved in this process.

- Management team:

This is a single team unit. The unit is organized in 4 major research topics each led by a researcher with teaching duty (3 MD PhD and 1 PhD). The head of the unit does not have his own research project. Decisions are taken by the head of the unit together with the four senior scientists. There is no specific management committee for the unit, but also no obvious need to have one. The senior scientists including the director of the unit are applying for funding in a concerted and rather successful manner.

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

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1,2	1,2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	2,8	3,5
N6: Number of Ph.D. students (Form 2.7 of the application file)	5	2
N7: Number of staff members with a HDR or a similar grade	5	5

2 • Overall appreciation on the research unit

- Overall opinion:

INSERM U853 is an internationally recognized research group in the field of Helicobacter pylori pathogenesis and has significantly contributed to the knowledge we have on this fastidious bacterium. It is a relatively small research unit well integrated in the dynamic context of the campus of the University Bordeaux 2. The group has set up numerous collaborations with clinicians and with other research units in different fields related to Helicobacter infections and to other diseases of the digestive tract.

The research is organized in four different topics each guided by a university professor or assistant professor. Their major focus is on two important issues in the field: the Malt lymphoma and the gastric carcinoma. The team is addressing these questions by combining multiple approaches, like epidemiology and the study of clinical samples, genomics of Helicobacter, animal models, cell biology and immunology. The friendly atmosphere within the unit allows strong interactions between the different groups and the sharing of the different expertise. Furthermore, the team is ready to collaborate when expertise and technological knowledge are missing.

The scientific production of the unit is good in terms of number of publications [50 per reviewed international publications, in very and good specialized journals (7<IF>2: Gut(3), Am J Gastro (1) Emerg Infect Dis (2), J Infect Dis (2), PloSOne (1), Infect Immun (1), Antimicrob Agents Chemother (1), J Antimicobial Chemother (3), J Pediat (1), Biol Scie (1), J Clin Microbiol (3), Eur J Clin Microbial Infect Dis (1), Clin Microbial Infec (1) Helicobacter (5), Exp Biol Med (1)]. The impact and international visibility of team is also attested to by the invitation of the head and members of the Unit to speak at international meetings (28 oral presentation in meetings),to publish review articles speciallized journals in: Helicobacter, Amer J Gastroenterol, J Cancer, Clin Microbiol Rev, Gastroenterol, Lancet Infec Dis). However the large number of projects, considering the size of the unit, preclude in most cases in depth analyses and publication in high ranking journal. The unit has also a strong involvement in teaching and public understanding of science.

- Strengths and opportunities:

The main strength of the unit is the number of collaborations it has set up with clinicians, with research laboratories and with platforms. In particular the association with the National Reference Centre for Campylobacter and Helicobacter represents an essential source of bacterial strains and of interaction with clinical microbiologists. The research performed is at the frontier of translational research and fundamental research. This unit has a strong international reputation in the research field of chronic *Helicobacter pylori* infections, leading on the one hand to neoplasia (both adenocarcinoma and maltoma) and on the other hand to chronic atrophic gastritis. This particular aspect of Helicobacter infections is extremely difficult to study experimentally.

The research performed within the unit combines animal models, molecular biology and more recently cellular biology. The combination of these different approaches allows the unit to address key questions in understanding the physiopathology of chronic Helicobacter infections.

The management skills and the international reputation of the director of the unit is also a major strength contributing to the dynamism and the visibility of the unit. The unit has been rather successful in obtaining financial support from different national (French cancer and gastrointestinal fundings) international institutions (FP6) and pharmaceutical companies and to attract PhD and master students which are essential to conduct the proposed research projects.

The unit proposed to conduct several projects with high scientific potential, particularly in the field of MALT lymphoma and gastric cancer. These projects represent opportunities to perform breakthroughs in the field.

- Weaknesses and threats:

The major weakness of the unit is the dispersion of the research projects into multiple topics. Each senior scientist proposes several ambitious projects, which she or he expects to conduct with only few students. There is a threat that each project will only be superficially treated without addressing the really important questions. The dispersion of the past research activity explains in part the small number of publication in high impact journals.

The five permanent scientists of the unit have teaching duties and four are MD PhD with diverse specialties (clinical microbiology, gastroenterology, geriatric). This represents a strength, but also a threat in terms of a lack of diversity in how to address questions. Thus the unit misses full time researchers, although this is partially compensated by the recruitment of students and postdoc fellows.

- Recommendations to the head of the research unit:

The diversity of the topics addressed in the unit and the numerous collaborations with clinicians is one of its richness and represent the basis for addressing the mechanistic aspects of the pathologies. This should be preserved. However, the head of the unit, together with senior scientists should better define a smaller number of key questions. In particular the unit should further move from exploratory and descriptive research towards more in depth explanatory research.

In addition to a strategic selection of few projects with high potential, the unit should seek to attract or recruit full time researchers to get the required human ressources for their ambitious objectives.

- Data on the work produced:

(cf. http://www.aeres-evaluation.fr/IMG/pdf/Criteres_Identification_Ensgts-Chercheurs.pdf)

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	5
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	1
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	1
A4: Number of HDR granted during the past 4 years	1
A5: Number of PhD granted during the past 4 years A6: Any other relevant item in the field	5

3 • Specific comments on the research unit

- Appreciation on the results:

The members of the INSERM U853 research team study an important public health problem, *i.e.* human infections caused by bacteria of the *Helicobacter* species. Their aim is to unravel the molecular mechanisms by which these bacteria cause diseases ranging from ulcer to cancer.

The bulk of the research activity is on *H. pylori*, with a side project focusing on enterohepatic *Helicobacter* species.

The main project aimed at identifying factors associated with the induction of ulcer or mucosa-associated lymphoid tissue (MALT) lymphoma has led, using an array of different approaches, to the identification of marker genes associated with strains causing peptic ulcer disease in children (*homB* gene) or with MALT lymphoma strains (e.g. ORF JHP950). However, very little progress has been made in identifying the function of these genes and the corresponding proteins. The team also participated in the annotation of a MALT lymphoma strain (B38, unpublished) in collaboration with the Pasteur Institute in Paris. A novel and very ambitious program, with good potential to lead to results that may have a high impact on the community, is at the interface with cell biology and aims at understandingthe cellular mechanisms leading to *H. pylori*-induced gastric cancers. A suitable animal model was designed to study the possibility that *H. pylori* virulence factors might promote the conversion of mesenchymal stem cells into cancer stem cells. Preliminary results are currently being analyzed. This certainly constitutes a turning point in the research of this unit, which perfectly fits in the concept of interface between fundamental and translational

research. Finally, there was a small and purely clinical project analyzing the effect of *H. pylori* on ageing people. Thanks to the collaboration with clinicians, the unit has the opportunity to study the effects of chronic infections in cohorts of elderly people. This may allow to identify new targets for further mechanistic studies.

A second smaller area of research is dedicated to the study of the potential role of enterohepatic *Helicobacter* species, such as *H. hepaticus* and *H. pullorum*, in liver carcinogenesis or inflammatory bowel disease. The first project is recent, well-designed and aims at understanding the potential cumulative effects (with respect to hepatocellular carcinoma) of infection by *H. pullorum* and the hepatitis C virus. The second project is more clinical in nature and studied the pro-inflammatory potential of *H. pullorum*, trying to link it to common inflammatory bowel diseases, most notably Crohn's disease.

Overall the committee felt that the quality of the research is acceptable but could be improved by a better focus on fewer research questions and a more profound follow up characterization of the interesting genes and/or proteins identified so far.

Steady publication output: 31 research papers and 33 reviews or comments, on most of which members of the group are either first and/or last authors. Quality is acceptable but could be improved since research articles are mainly in specialized gastroenterology/*Helicobacter* journals, one of which (Gut) has a medium impact factor, and occasionally in general microbiology journals with impact factors in the lower range.

Excellent scientific communication with 28 oral presentations and 45 posters at national and international meetings.

Excellent performance in student supervision: 4 PhD theses have been completed between 2005 and 2008, 3 are under way. In addition, 17 Master students, 6 Licence students, 10 IUT/BTS students have done practical courses in the lab.

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

After 20 or so years of commitment to clinical and fundamental research on *H. pylori* infections in humans, the group has a strong reputation - as attested to by (1) numerous invitations to speak at international congresses/symposia on gastroenterology and infectious diseases extended to its Director (along with the organization of events by the group), (2) its status as a reference centre for most of the clinical trials on treatment of *H. pylori* infection being performed in France and throughout Europe and (3) its Director's work on the Editorial Boards of several learned journals (BMC Gastroenterology/Gut Pathogens, Helicobacter, Clinical Microbiology and Infection).

Via its affiliation with the University, the group's mission's includes teaching students and training undergraduate interns and postgrad research students. Around fifty or so of the latter have been hosted for various periods over the last 4 years. Five have obtained a PhD and each doctoral student featured as an author (and often the lead author) on an average of two original research articles, together with various presentations at congresses/colloquia/symposia. The research training activity currently involves a French postdoc and 3 doctoral students. One of the latter is set to defend his thesis very soon and is set to start a 3-year postdoc contract in a very well regarded Australian lab. In the Director's opinion, this will be of great value if the individual subsequently chooses to apply for a staff researcher position in INSERM Unit 853; in the recent past, two other candidates have unsuccessfully applied for this type of job.

In view of the carcinogenic potential of *H. pylori*, the group has received substantial research funding (almost 500 k€) from French cancer and gastrointestinal disease charities, the EU's Sixth Framework Programme (FP6) and the pharmaceutical industry.

The group, which is the National Reference Center for *Helicobacter* (since 1993), is included in a European consortium of *Helicobacter* research labs.

Even though the research has generated medically useful outputs, no patents have been filed over the last 4-year period.

- Appreciation on the strategy, governance and life of the research unit:

INSERM U853 is a small unit with the adequate organization. Most decision are take by the head of the unit in tight interaction with the four other scientists with permanent position. Principal investigators for grant applications are either the head of the unit or an other scientist. Although most of the external communication is performed by the head of the Unit, the whole Unit has an national and international recognition and contribute to the communication. During the visit no problems were identified in the organization of the unit and both students and "ITA" are satisfied and enjoy working together.

The unit has initiated numerous projects with high potential. A strong point of the unit is the development of such project on the basis of clinical data or observation. All scientists are implicated in the emergence of these projects. However, as pointed in different parts of this report, one issue is the too high number of such risky projects.

The unit has a strong involvement in teaching activities as the five scientists with permanent position have teaching duties both at the medical and at the scientific faculties. The unit contributes also to the public understanding of science, which is particularly relevant in the case of *H. pylory* and the numerous diseases it causes. By the number of collaborations, the unit is perfectly integrated in the University of Bordeaux II research campus.

- Appreciation on the project

Projects are ambitious long term projects. The main point that the committee raised is the limited man power with respect to the ambitious projects proposed. This group should focus on some aspects of their projects in order to perform more in depth analyses that should allow them to perform significant breakthrough in the field and to publish in journal with higher impact factor. Most of the full-time man power is dedicated to axe 1, which should help to achieve their goals.

Axe 1 : Helicobacter pylori

Helicobacter pylori and gastric MALT lymphoma

This project is aimed to indentify new genetic markers for strains associated with gastric Malt lymphoma by comparing the genome of 3 strains. This part is ambitious and might be facilitated if the team interacts with specialist in bioinformatics. As a follow-up of the genomic approach, it is proposed to study in a murine MALT lymphona model, the role of known virulence factors and newly identified genes associated to MALT strains. The combination of these two approaches should allow to progress on the mechanism by which infection by some strains of H. pylori give raise to gastric MALT lymphoma. Due to the size of the team it could be important to limit the study to these two aspects. The study of the role of dendritic cells in the pathology of gastric Malt lymphoma is certainly very important but probably difficult to achieve together with the two other analyses by two persons.

Study of gastric carcinogenesis

This project is aimed to identify cancer stem cells in the mouse tumors that apparently mimic the human tumors as well as in a collection of gastric tumors by testing candidate markers of cancer stem cells. The team has recently shown in a mouse model that mesenchymal stem cells from bone marrow (MSC) can colonize the stomach upon H. pylori infection, confirming independently for the first time a previous work, which had a high impact. The committee recommends to validate the importance of MSC in human gastric carcinoma by looking for specific markers of these cells in their collection of murine and human gastric tumors prior to determine how the presence of MSC in stomach predisposes to cancer. A second aim is to study IQGAP1 in epithelial-mesenchymal transition and gastric tumor. This is a large and complicated field. Because of the small number of investigators (one PHD student and its director) the committee recommends to focus on the specific question regarding how IQGAP1 participates in gastric tumor.

H. pylori and Alzheimer's disease

This project is aimed at studying the impact of H. pylori infection on the development of Alzheimer's disease. Similarly to the above mentioned projects, this is a risky and long term project that combines long term infection of mice and intervention studies in humans, potentially leading to man power dispersion. The committee believes that this project should focus on the human intervention study prior to dedicating any man power to mice studies.

Axe 2 : Enterohepatic Helicobacter

HCV-H. hepaticus coinfection

This project is an example of a project that was further focused probably due to the small man power allocated. The future project is presented as if the association of HCV-H. hepaticus was demonstrated. In particular, the team proposes to study the cellular modifications involved in hepatic carcinogenesis. Due to the reduced man power allocated for the moment, all efforts should be dedicated to show a clear synergy between HCV and H. hepaticus. In particular, it is highly recommended to pursue the study of the potential virulence factors described, since the group is clearly specialized in microbiology and has only an emerging expertise in cell biology.

IBD and H. pullorum

A clinical study regarding the implication of H. pullorum in chronic inflammatory diseases of intestine has been initiated. In parallel the team plane to explore the toxicity of the cytolethal distending toxin from H pullorum on culture of intestinal cell to this goal the propose to directly produced the toxin in cell line derived from colon adenocarcinoma. This is a focused project with realistic aims that should help elucidate the potential implication of enterohepatic helicobacters in human disease. Up to now this group succeed to national and international grants. The main point that the committee raised is the limited number of investigators in relation to the ambitious projects proposed. This group is one of the first in France that study this important pathology. A strong point is that they are working in collaboration with clinicians and that they have important connections with the national and European community studding helicobacter. The risk taking should be limited if the team combine genetic screening with molecular and cell biology as well as study on human tumors.

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 Pierre GLORIEUX
Directeur de la section Unités de recherche
AERES

Bordeaux, le 22 mars 2010

Monsieur le Directeur,

Je vous transmets les observations de Monsieur Francis MEGRAUD, Directeur de l'Unité « Infection à hélicobacter, inflammation et cancer », faisant suite au rapport du Comité de visite de l'AERES.

Je vous prie de croire, Monsieur le Directeur, à l'assurance de mes sincères salutations.

Le Vice-Président du Conseil Scientifique,

Alain BLANCHARD

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Reply to the AERES Committee Visit Report on INSERM Unit 853

First, the Director and the personnel of U853 would like to thank the Committee for their commitment and time spent to visit our Unit as well as for their pertinent recommendations.

We are happy to see that most of the points that we considered as strong points are indeed acknowledged as such by the Committee:

- importance of the subject studied
- international recognition of our work
- synergism with the National Reference Center for Campylobacter and Helicobacter
- strong links with clinicians on projects at the interface between basic and translational research.
- important collaborations at different levels
- important involvement in teaching
- positive atmosphere existing between the different types of personnel

- However, a major criticism is **the dispersion of research projects**. Indeed, we have 2 major projects to which the majority of our resources are devoted: one concerns gastric MALT lymphoma in relation to the type of *Helicobacter pylori* strains involved, the other concerns gastric adenocarcinoma with an emphasis on stem cells.

It is true that we also presented side projects on Alzheimer's disease and *H. pylori* as well as IBD and enterohepatic Helicobacters. These projects are overseen by Professors of Medicine who were seeking our collaboration to develop projects in our area. This remark indeed poses the problem of integrating clinicians in research units. We think that it is our duty to give them an environment where they can

develop their own projects, obviously related to ours, which will have a positive impact on their teaching responsibilities and on
the University as a whole. In fact, the resources of the Units devoted to these projects are limited and we consider that we also benefit from their presence in several ways. With due respect for their work, we decided to present these projects but probably we were not clear enough on hierarchizing our activities.

- The recommendation of the Committee was **to go more in depth in the mechanistic aspects of our projects** and we definitely share this opinion. Concerning gastric MALT lymphoma, the *in vivo* project constitutes indeed the main axis of our research strategy. We will have the opportunity to link the *in vivo* response to the genetic content of the strains recently sequenced (one publication already submitted, and another that will be submitted in the following months). This research part is very ambitious and require long time infection period. We are currently verifying the infectivity of our strains in our mouse model. During all the preliminary steps, we therefore focus on the *in vitro* interaction between *H. pylori*, dendritic cells and lymphocytes. We already have promising results that we aim to publish for the end of the year. Therefore timing will be perfect for the next two years to achieve our project. C. Varon is also looking in depth at the characterization of cancer stem cells in gastric carcinoma due to Helicobacter infection. After having developed a mouse model involving mesenchymal stem cells as a source of cancer stem cells (CSC) in gastric carcinogenesis due to *H. pylori* infection, she is planning to go further and to characterize CSC in human tumors by developping a mouse model of human tumor xenograft which, according to the canceropole Grand Sud Ouest, is unique in France for gastric adenocarcinoma. These two models will allow the study of candidate molecules and cellular targets like IQGAP1 in gastric cancer.

- The **publications of the Unit are judged by the Committee as "acceptable"**. It is true that we had a limited number of papers in journals with a high impact factor. The reason, which we would like to highlight, is that this visit was not timely for us. No publication was derived from the major project on gastric adenocarcinoma begun 3 years ago when the Unit was launched, while most of our resources were dedicated to it. The important work achieved in a new area for us is now arriving at its term. C. Varon began to present the first results which were appreciated enough for her to be invited to present them at the next United European Gastroenterology Week next October and several papers will be sent to high impact factor journals before the end of the year.

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- We definitely share the opinion of the Committee with regards **to the need to recruit a full time researcher**. Indeed, as was noted, over the past years, we were contacted by 2 French post-docs working in the US and interested by our activities. Both of them presented themselves as candidates for an INSERM CR2 position but, unfortunately, failed to be recruited. Our future aim will be to recruit a full time researcher. We have hope that a former PhD student from our group, J. Ferrand, who is particularly brilliant, will be more successful in returning after his post-doc in Australia. With regards to other personnel such as engineers and technicians, we have secure funds to allow us necessary recruitments according to the needs of the projects.

In summary, we will follow the recommendations of the Committee in developing only 2 major projects, each of them in a more focused manner, to get more in depth knowledge. Our resources will be focused on these projects and so we will increase the chance to publish in journals with higher impact factors and we will do everything possible to recruit a permanent full time researcher.

Université Victor Segalen Bordeaux 2

INSERM ADR9

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