Foie, métabolismes 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

Foie, Métabolismes, Cancer

From the

Université de Rennes 1

Inserm

December 2010

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

December 2010

Research Unit

Name of the research unit : Foie, Métabolismes, cancer

Requested label: UMR S Inserm

N° in the case of renewal: UMR S991

Name of the director: M. Bruno CLEMENT

Members of the review committee

Committee chairman

M. Robert BAROUKI, Université Paris-Descartes, Paris, France

Other committee members

Mme Béatrice DESVERGNES, Université de Lausanne, Lausanne, Suisse

Mme Ariane MALLAT, Université Paris Est Créteil, Créteil, France

Mme Marie Paule ROTH, Université Paul Sabatier, Toulouse, France

Mme Valerie PARADIS, Université Paris Diderot, Clichy, France (CSS Inserm 6)

Observers

AERES scientific advisor

M. Pierre LEGRAIN

University, School and Research Organization representatives

M. David ALIS, Université de Rennes 1

M. Raymond BAZIN, Inserm

Report

1 • Introduction

- Date and execution of the visit

The visit took place on December 7th, 2010. It started by a short meeting of the committee. This was followed by a general presentation by the Unit head describing the history of this new unit and the general strategy. Then, each team concisely presented and discussed its past achievements and its projects for approximately 30 mn. Presentations per se lasted for half of the time and the other half was left for discussion. The committee met with local and national representatives (University, faculties, Inserm, etc.) and with the research scientists, technicians/engeneers and students/post docs. An internal meeting of the committee members took place to discuss the evaluation report

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

This application is for the renewal of the Inserm and university support and funding to unit 991 which was officially established on January 2010. The reason why this application had to be filed after such a short period is that the whole university is under examination by the AERES this year and, therefore, it was considered that all the university units should be examined (or reexamined) at the same time. Clearly, the nine month period is not sufficient to evaluate the performance of unit 991. Thus past activity was extended to that of the previous units constituting unit 991. This unit resulted from the gathering of Inserm units 620 and 522 (Rennes), as well as a group of unit 773 from Bichat, Paris. In addition, scientists from two university units joined the project.

The primary expertise field of this unit is liver biology and pathology. Clearly this unit gathers excellent researchers with this expertise. As will be mentioned later, the unit establishes very strong ties with the liver and GI departments of the university hospital. However, the management of the unit has extended clinical ties with other departments including cancer, radiotherapy, rheumatology, nutrition, endocrinology and metabolism.

- Management team

The unit is managed as recommended for Inserm units. It is managed on a daily basis by the unit Director who is supported by the board of team directors. Important decisions are taken by the lab committee which meets 3 to 4 times a year. An external scientific committee is also expected to be formed and to provide comments and advice on the long term unit scientific orientations. From the visiting committee discussions with the personnel, it appears that there is a general approval of the management of this unit.

- 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)	19	24
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	11	11
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	18	17
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	8	9
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	4	
N6: Number of Ph.D. students (Form 2.7 of the application file)	26	
N7: Number of staff members with a HDR or a similar grade	26	31

2 • Overall appreciation on the research unit

- Summary

The unit consists in four teams each one with a clearly identified project and history. All teams have in common a focus on liver biology and pathology, but their projects also include items with impact in other pathological or physiological systems. Team 1 has a highly recognized expertise in iron biology and in liver diseases related to iron overload. Team 2 carries studies on hepatocyte diifferentiation, proliferation and stress responses and has developped very useful liver derived cell lines. Team 3 is focused on liver toxicity mechanisms and has an ambitious project on the interaction between obesity and xenobiotic toxicity. Team 4 has a unique expertise in liver cells microenvironment and its implication in liver carcinogenesis. Several projects arise from at least two teams, for example, detoxication mechanisms and obesity, biology of hepatocyte proliferation, and system biology of iron in liver.

- Strengths and opportunities

- One of the main strengths is the quality of the team projects and of the inter-team projects. These projects are timely and are in line with the unit general orientation. All these projects are supported by basic studies and, in most cases, have a clear orientation towards translational medicine.

- There are several projects which involve scientists from different teams as mentioned in the summary. Clearly the policy of the unit has been to foster such collaborative studies and this is a good « raison d'être » of this unit.

- Valorisation of the research is also a strength. This is clear from the numerous interactions between the scientists and the clinical departments (several MD and PharmD are members of the unit). In addition to clinical valorisation, the unit has also developped biotechnological applications (for example the development of the HerpaRG cell system in toxicology as well as the cellular platform).

- Management is also an obvious strength. This is illustrated by the following achievements. During the last years, the Inserm units in Rennes have been restructured leading to a period of relative instability. Clearly, a new organization has now been achieved and it appears to fulfill the scientists expectations allowing them to go ahead with their research. The management deserves at least some of the credit for that. In addition, the unit has been able to sustain its expertise in liver biology and pathology and, at the same time, to develop solid interactions with other

clinical departments. This is certainly an important achievement for the future which sets the unit as a critical template for translational medicine in the Rennes medical community.

- The international recognition of several scientists in the unit is certainly a great asset. This is manifested by the numerous invitations to national and international meetings.

- The unit has been able to identify young leaders with high potential. It should now help these young scientists establish international networks.

- The scientific production of the unit is well balanced among teams and can be considered good to very good. Publications are in some of the best journals of the field.

- The ability to raise funds is also remarkable.

- There is a very good interaction between research and teaching.

- There is a very strong local support to the unit from university, medical and pharmaceutical faculties, cancer department, etc.)

- Weaknesses and threats

-Although the publications are in some good to very good journals of the field, the committee believes that with the quality of the projects and the interaction with the clinics, publications in journals with higher impacts should be possible, particularly with the stability of the team organization that is now expected.

- The number of projects in some of the teams is relatively high. These projects can be better prioritized.

- The physical separation of one of the teams can be an issue in the long run. This is expected to be solved in the near future

- Recommendations

- A trivial recommandation would be to attempt to publish in higher impact journals. In the case of this unit, this seems achievable most probably through the interaction between basic and clinical sciences that is already present within the unit.

- Diversity of projects is a threat to any unit. The management should make sure that all projects are within the orientations of the unit and should not hesitate to reassess the priority of the projects on a regular basis. The scientific committee could help in that respect.

- The unit should keep its efforts to recruit young scientists and to help its own young scientists establish international networks.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	19
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	11
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	1
A4: Number of HDR granted during the past 4 years	2
A5: Number of PhD granted during the past 4 years	26

3 • Specific comments

- ## Appreciation on the results

A detailed appreciation of the results is given for each team. During the preceding term, the unit has made some significant findings. Some of these findings would not have been possible in the absence of good interactions between two or more teams. To illustrate these interactions, the committee noted the following projects: characterization of hepcidin gene regulation and functional genomic study of the effect of iron overload; characterization of critical players in hepatocyte proliferation and differentiation such as the cyclin/cdk system, GSTs and proteins of the microenvironment; further characterization of the HepaRG cell system and its application in predictive toxicology and iron biology; toxicity of drugs in the context of steatosis and obesity; role of the Wnt/catenin system in the signaling of a variant of collagen C18 variant.

The scientific production is good to very good. The unit publishes its work in very good journals of the field such as Gastroenterology, Hepatology, J Hepatol, J Clin Oncol, Oncogene, Tox Applied Pharmacol, Am J Physiol, etc. They have filed several patents and contributed to the constitution of several platforms.

They have established local, national and international partnerships.

As a whole the production of the unit is very good. This production is in fact balanced between the different teams.

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

Several scientists of the unit have a well established internationally reputation: they have been invited to international conferences and in some cases organized international meetings

The unit has a remarkable ability to raise funds: EU, ANR, cancer, etc.

They have established networks that are related to the European consortiums.

Some of the younger scientists should improve in the future their international networking. This should be facilitated by the connections established by the more senior scientists.

- ## Appreciation on the management and life of the research unit

Discussions with the different personnel of the unit revealed a general support for the management initiatives concerning the scientific life of the unit, its administrative organization and its support for career progression. Some difficulties remain due to the geographic location of one of the teams and to the status of some of the personnel.

The management took some important and quite positive initiatives in the last years. First, the management organized teams that are project oriented and that originate from different previous units, which is quite positive for the cohesion of the units. Second, the management established links with new clinical departments while still strengthening its traditional links with the liver disease department. Third, the management encouraged translational research projects and supported the implication in platforms and biobanks. Thus, the action of the management even in a very short time is already visible and this is a strong asset of the unit.

Several members of the unit are faculty members and are directly implicated in various aspects of teaching and educational organization at the local and the national level.

- ## Appreciation on the scientific strategy and the project

As can be seen in the discussion of each team project, this part is one of the major assets of the unit. There are clearly some very exciting projects in the field of iron metabolism, proliferation of hepatocytes in the context of their microenvironment and the interaction between toxicity and metabolic state and obesity, to cite just a few. The management of the unit and of the teams should keep focused on few top level projects. The unit allocates part of its budget to the initiation of new collaborative projects or proof of concept projects that could not be easily funded otherwise at an initial stage.

4 • Appreciation team by team

TEAM 1: Fer et Foie: aspects physiologiques et pathologiques

TEAM LEADER: Olivier LOREAL

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	8	8
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	5	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	
N7: Number of staff members with a HDR or a similar grade	10	10

- Appreciation on the results

Team 1 focuses most of their scientific efforts on the molecular mechanisms by which liver maintains iron homeostasis and the impact of genetic/exogenous factors on this regulation. Iron research has always been a hallmark of Rennes both from a clinical and an experimental standpoint, and the head of the actual group is well known for his discovery of hepcidin role in the regulation of iron metabolism in 2001. Within the general framework of hepcidin research, members of this team have conducted during the last five years multiple but relatively medium-term projects exploring new research avenues for the years to come. They have carried out basic work on hepcidin regulation, exploring consequences of stimuli like venesections, inflammation, muscular activity, thalassemia or dysmetabolic syndrome. This has led to several publications in medium IF journals (BBA 2008 & 2010, Haematologica 2008, Eur J Physiol 2009 and J Mol Med 2010). They have also carried out transcriptomic studies to find new genes associated with iron metabolism but the physiological importance of these regulations will be addressed in future projects.

Impact of iron overload on osteoporosis is an interesting and so far poorly investigated issue. The recent arrival of a young rheumatologist in the group is perceived as a very positive event. This scientist has proved his ability to explore bone morphology and modifications induced by iron-overload, both in genetic hemochromatosis and in a murine model for this disease. Two papers in Metabolism Clinical and Experimental in 2008 and Osteoporosis International in 2010 are directly related to this work.

Some members of the group have a long-term experience in the characterization of iron chelators and the possibility that polyamines combined to iron chelators targeted to tumor cells could impair their viability and proliferation is interesting. This project however could progress more rapidly (publications in Biometals in 2006, Eur J Pharmacol in 2006 and Cell Prolif in 2007) and may need reinforcement to be more competitive.

The active participation of clinicians has also allowed the characterization of mutations in HFE and FPN1 through functional studies, the investigation of phenotype/genotype relationships and the identification of a non genetic cause of aceruleoplasminemia-induced iron overload. This should help better understanding the function of these molecules in the iron-regulatory pathway and has led to publications in Haematologica (2009), Blood (2010) and Gastroenterology (2010). Those studies are excellent illustrations of the translational research going on in the team.

In addition, clinicians have conducted several significant therapeutic projects in the field of iron overload (Hepatology 2006 and 2010).

Three PhD students have prepared their theses in the team during the last five years. Importantly, the three of them have participated in national/international conferences in the field of iron and have all presented posters/oral communications.

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

The team leader and the two senior clinicians are internationally very well recognized in the field of iron and, together, have been invited to a total of 65 conferences/symposia during the last five years. They have been successful in raising not only regional and industrial funds but also a competitive European grant on the genetic control of the pathogenesis of diseases based on iron accumulation. Two key scientists of the team were the joint coordinators of this grant which included 11 partners.

- Appreciation on the scientific strategy and the project

The scientific project is a follow up of their previous work, and is therefore equally interesting and diverse. Members of this team need to identify a small number of projects they want to focus on and put most of their strengths on these in order to bring them to a competitive level. Using their original coculture model as well as mouse models, they may be able to elucidate the role of Atoh8, a transcription factor, in the regulation of iron metabolism and to pinpoint an important element of the regulatory pathway. The possible role of hepatic hepcidin in the modulation of inflammation is puzzling and certainly warrants further development. Finally, arthritis and osteoporosis are two common complications of iron-overload disorders and the mechanisms leading to these complications are not yet understood. The project on the impact of iron excess on the osteoblastic/osteoclastic balance and bone remodelling is therefore original and potentially promising. Clinically-oriented projects deal with important unanswered questions such as the identification of patients at risk of complications, the development of non invasive diagnostic tests and the role of iron chelators or novel hepcidin modulators in the management of iron overload and could be pursued at the previous pace

- Conclusion :

  - Summary

This is a solid team. The past and present performance is of international standard for the field.

  - Strengths and opportunities

Integrated project including fundamental, translational and clinical aspects. Both the fundamental and the clinically-oriented topics are of significance, original and are worth being actively pursued. There are sound models in place to investigate hepcidin regulation further and explore its possible role in the modulation of the inflammatory response. There is, in addition, a clear translational effort incorporated in the research focus that relies on the local major databases of patients with genetic hemochromatosis and dysmetabolic hepatosiderosis and on a good recruitment of patients suffering from rare iron-overload diseases through the Centre National de Référence implemented locally.

The novel topic of the research on the mechanisms of bone complications of iron overload has a potentially important clinical impact.

International leadership of team leaders and established national and international collaborations.

  - Weaknesses and threats

There are many projects and they are not prioritized enough.

The two senior clinicians in the group are internationally recognized for their work on iron-overload disorders and the management of such patients. It is very important that this Rennes specificity be maintained after they retire and they should therefore identify and train potential successors as soon as possible.

– Recommendations

The team has a unique expertise and important projects. Since one of the threats is the diversity of projects, the major recommendation is to set precise milestones for each project for the evaluation of results and achievements. Depending on these evaluations, strategic decisions should be made in terms of which research themes may be pursued, expanded or stopped. This will be essential to increase the level of competitiveness of at least a few of their many projects.

TEAM 2 : Stress, défenses et régénération

TEAM LEADER : Fabrice MOREL

- Staff members

	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)	4	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	5	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	3
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	3	
N6: Number of Ph.D. students (Form 2.7 of the application file)	10	
N7: Number of staff members with a HDR or a similar grade	7	7

- Appreciation on the results

Team 2 is composed of three groups that focus their research on the fundamental aspects of hepatocyte proliferation and differentiation, their link to stress responses and the evaluation of corresponding new therapeutic approaches. A fourth group is carrying a transversal project, developing a platform of innovating cellular approaches, extremely useful not only for this team but for all the other teams of the Unit.

The project is based on new interesting links recently unraveled and explored by the team members. For example, the solid research program concerning the role of GST in detoxification is now broadened to new properties activated upon hepatic regeneration and oxidative stress, completed with the new characterization of the GST kappa class. Detailed molecular studies of how the main growth factors as well as the extra-cellular matrix remodelling contribute in controlling the hepatocyte cell cycle led to the re-evaluation of the role of Cdk1 in the S phase in human hepatocytes. Collaborations with clinicians allowed pursuing these molecular studies in the context of liver regeneration. The full characterization and exploitation of the HepaRG cells, isolated from a human hepatocarcinoma provides a very solid asset to the team and has authorized numerous studies concerning either hepatocyte proliferation and differentiation or chronic toxicity.

Due to the recent construction of the team, whose members come from two different Inserm units, a unifying summary of last years achievements is rather difficult. However, the outcome in terms of publications is very satisfactory, with a total of 84 papers with a certain number in medium to high IF. In addition, the valorisation of the HepaRG cells has been well managed, and technical developments that have been pursued around these cells have been very efficient, leading to both publications and establishment of a welcomed platform.

Altogether, the team has supervised 10 thesis during the last five years.

There are numerous collaborations, local and national, but also international (Italy, Japan, USA, Spain, Belgium, Netherland, and Tunisia), reflecting the importance of the research output of the team members.

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

The main leaders of this team have been regularly invited to give seminars in an international context, often in Japan. Invitations to international conferences are less impressive and a better exposition of the members of this team to international conferences should be encouraged. National recognition is very well established.

The recent recruitment of three post-doctoral fellows in this team reflects well its attractiveness. Nonetheless, the efficiency in raising funds is the most telling. The team has partnership in 4 European programs, 2 of which ended up in 2009, and 2 are active until 2011 and 2013, respectively. These programs also illustrate the capacity of the team to generate and maintain active international collaborations. In addition, there are number of others financial supports from ANR (5 programs from 2006 to 2012), ARC, LNCC, international cooperation and industrial contracts.

As is also underlined in the comments concerning team 3, the socio-economic output is particularly remarkable with the research on the HepaRG cells.

- Appreciation on the scientific strategy and the project

Despite their recent construction as a team, the proposed project is showing very good integration of the diverse parts. The quality of the project is indeed a major strength of the team. In a solid and original project, the first group will use systematic molecular and cellular approaches to explore GST interactome and activities, particularly along the cell cycle. Specific interests in CdK1 and Cdk11 will be tackled by the second group, together with the studies of factors leading to hepatocyte final differentiation. This at least in part will merge with the European project LIV-ES. This project is very timely, open and of high potential implications, albeit not all part of the projects are equal. The third group is deliberately more clinically orientated and will benefit of the high quality of the fundamental research within the team to explore the best approaches for the preservation of the liver functions upon transplantation. Finally, the fourth group is technically oriented and will pursue the development of the platforms ImPACcell et SynNanoVect, for the benefit of the team, the Unit, and beyond.

Thus, the project goes from basic and molecular studies to technical development and clinical approaches, all being linked together via the focus on the response of hepatocytes to challenges affecting their ability to proliferate and differentiate. The questions put forward are of broad interest, the tools to be used and the general strategy are well appropriated.

The internal organization is well-thought, with 2 PI to coordinate each group, and a good balance between senior and junior researchers, as well as technical staff, PhD students and post-doctoral fellows. The competencies of each PI are well in accordance with the planned project. Together with the remarkable ability to raise funds, it makes the feasibility high.

- Conclusion :

  - Summary

The team was constituted two years ago and brings together fundamental researchers and clinicians in a project that the committee evaluates as solid and promising. The past and present performances of the team members, despite a local difficult context of re-structuration, are of international standard.

  - Strengths and opportunities

- The scientific questions are innovative, of broad interest, and with promising outputs; the molecular investigations are ambitious and of high quality

- The project presented by the four groups shows a good thematic coherence

- Despite being recently re-composed, the team gives a good sense of unity

- Clinicians have a direct access to tools and networks developed by the team; overall, the translational potential of most of the projects is good

- The ability to raise funds is remarkable

- The number of collaborations and integration in scientific networks is remarkable

- Furthering the development of the HepaRG cells as an unmatched cellular model tool to explore liver biology is of major importance for the international community

– Weaknesses and threats

- Not all sub-projects have the same potential. The team should remain focused on what the project title claims “Stress, defence, and regeneration”; milestone might be needed for that purpose

- A leader scientist who is carrying an important share of attractiveness is going to retirement. With that respect, the team will have to face this departure.

– Recommendations

- The team leader may need to fix milestones with the different groups to help keeping the research efforts along the main focus

- Exposure to international conferences with possible oral or poster communications should be encouraged at each levels, for developing the international recognition

TEAM 3 : Hépatotoxicité des xénobiotiques: mécanismes et modulation par l'obésité

TEAM LEADER : Bernard FROMENTY and Marie-Anne ROBIN

- Staff members

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

- Appreciation on the results

This is a young team that was brought together two years ago when the two research scientists that are the present heads of the team moved to Rennes and joined the unit. This incoming group joined another group from Rennes headed by the previous director of one the constituent units. Therefore, the last few years have witnessed

several changes in team organization and this has settled down recently. Despite its relative youth, this new team has already made some very interesting observations. The common theme is liver toxicity with three major directions: liver toxicity in the context of obesity or NAFLD, cellular approaches of predictive toxicology and cellular distribution of CYP2E1, a major player in drug and alcohol toxicity. Important findings were made concerning the liver toxicity of several drugs in animal models of obesity and steatosis; other important findings were made in the characterization of the HepaRG cells as a unique model for the assessment of liver toxicity in human.

The constitution of a strong and cohesive team in less than two years is an important achievement of the team and its scientists.

Another positive achievement was the ability of the team heads to include in their team a group of endocrinologists and metabolic disease specialists from the corresponding clinical department, thus opening a new translational research focus in line with their team projects.

Scientific production remained good despite the fact that all the changes that occurred during the last 4 years. The team published 75 ISI referenced articles in which it had a leading position for two thirds of them. These articles are published in good specialty journals: Antiviral Ther, J hepatol, JPET, Am J Physiol, Obesity, Toxicol Applied Pharmacol, DMD, Tox in vitro, etc. The clinical endocrinology group that joined the team has a very good publication record (Diabetes Care,, Diabetologia,…). There are also a number of review papers and papers dedicated to a larger audience. In the new more stable environment, it is expected that publication output will be even better (qualitatively).

As a long-range indicator, it should be mentioned that the 3 main scientists of the team (not including clinicians) have an H factor of 50, 36 and 19 respectively. This is an excellent achievement especially when age is taken into consideration.

The team has one patent during the period. However, it should be stressed that the work on HepaRG which had bee patented previously, is extremely important in terms of application in predictive toxicology.

There are approximately 10 local, national and international collaborations.

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

The three main scientists of the team have been invited to give talks at 23 different meetings and institutes, 10 of them being outside France. The three main scientists have been invited although with different frequencies.

Despite its youth the team attracted students and posts docs.

One of the team members is an internationally recognized expert in cellular toxicology and has been invited to participate or to head several funding committees. The other two scientists are widely known experts in mitochondrial origin of liver toxicity, which is the main reason for the invitations they all received.

The ability to raise funds is impressive: 9 grants among which, 1 European union grant, 3 ANR grant, 1 INCA, 1 Ligue contre le Cancer, etc. In multipartner grants, the members of the team are principal coordinators in 2 of them.

The existence of stable collaborations with foreign labs is illustrated by the EU grant.

As far as socio-economic output is concerned, one has to stress again the value of the work on the HepaRG cells (shared with team 2). The studies that are currently carried on this cell line within the team will assess its value as a model for liver toxicity. This is critical at a time when more in vitro toxicity tests are needed because of ethical, practical and social reasons.

- Appreciation on the scientific strategy and the project

The team project is clearly one of its main strength. Western as well as developing countries are experiencing an obesity epidemics since several decades. An important issue is the interaction between xenobiotic toxicity and obesity, NAFLD or more generally metabolic diseases. This is tackled by the project by focusing on the assessment of toxic effects of chemicals in animal models of obesity and in animals with liver steatosis. The project also includes a clinical study with similar aims, as well as studies in the HepaRG model. The project on CYP2E1 expression and regulation is also of interest as this CYP is regulated by insulin and obesity and also because it accounts for the toxicity of some of the most relevant liver toxicants. However, this project should remain within the general focus of

the team on liver toxicity and should use cell biology approaches only in that respect. Another important aspect of the project is the study of chronic low dose effect of chemicals. This is one of the most challenging issues in modern toxicology. The HepaRG model system will likely allow such studies to a certain extent. In this respect, the team should be careful not to engage into routine tests, but rather keep its edge in mechanistic studies that could be transferred to more routine oriented labs.

Clearly the project is original and will keep the team busy for the next 5 years. Based on the ability of the team to raise funds, it should be able to carry the project appropriately.

- Conclusion :

  - Summary

The team was constituted two years ago. The fusion of the different groups was successful which reflects a wise leadership. The team focuses on different highly relevant aspects of liver toxicity in both in vitro and in vivo models as well as in human.

  - Strengths and opportunities

The major strength is the timeliness and originality of the project. Clearly the interaction between obesity, metabolic diseases and xenobiotic toxicity is novel and is worth studying. In additio the focus on long-term, low-dose effects of chemicals in an in vitro medel system is relevant.

The leadership of the team is another of its main strength. The leaders succeeded in developping a strong project. They were able to bring together scientists from different backgrounds and did that successfully. They were able to establish novel and releavant collaboration with clinical departtments involved in metabolism, nutrition and endocrinology which is an asset for the whole unit. The team is expected to grow steadily.

International recognition is also an important asset.

The ability to engage into clinically-oriented or biotech-oriented translational research is also an asset for several members of this team.

The team has been successful in raising funds

If it remains focused on its projects, the team has a unique opportunity to become one of the most recognized teams in liver toxicity nationnally and world-wide

  - Weaknesses and threats

The publication record of the team is quantitatively excellent but could be improved qualitatively. Now that the team is in a more stable condition, it should be able to publish in higher ranking journals.

The projects are extremely interesting but they should remain focused on liver toxicity mechanims. This is clearly the policy of the team and it is not a weakness at this stage, but it is clearly a threat.

  - Recommendations

The project is one of the main strengths of the team. However, as mentioned, there are possible threats. For example, the team should avoid engaging into routine in vitro studies despite funding temptations. It should focus on transfering these technologies to other routine-oriented or spin off labs. The team should remain focused on toxicity issues because of its background and expertise and avoid more basic cell biology issues in which other competing labs may be stronger (CYP2E1 project for example).

The committee is confident that with the new organization, the publication record of the team will improve.

International networking is an asset, but it should be strengthened and improved particularly for the younger scientists and in the most promising fields that are developped such as obesity.

TEAM 4 : Remodelage du microenvironnement et progression du carcinome hépatocellulaire

TEAM LEADER : Bruno CLEMENT

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	5	8
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	6	7
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2	2
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	
N7: Number of staff members with a HDR or a similar grade	6	9

- Appreciation on the results

The team, managed by the head of the unit, gathers multidisciplinary staff members coming from former Unit 620, 2 university units and clinical departments from the CRLCC. Such composition, further divided into 2 groups, results in a fundamental project with significant clinical applications in terms of development of biomarkers and biotherapies in the context of hepatocellular carcinomas (HCC).

The main objective of the team, dedicated to the study of the microenvironment remodeling of HCC, is original and poorly investigated so far. This project is based on original basic research data obtained by the group over the past years (1997-2001), showing involvement of metalloproteases and extracellular matrix components, especially collagen 18 (C18), in liver fibrosis and remodelling of HCC. Importantly, they recently identified one variant of C18 through a frizzled receptor (FZC18) being able to suppress Wnt/ ß-catenin activity (Plos one 2008, Oncogene 2010). In order to better understand the role of microenvironment in development and progression of HCC, and identify new bioactive targets, a comprehensive and integrative genomic study of HCC stroma is developed mainly thanks to the access to different platforms (Biobank, ImpACell,…). This objective is also supported by a post-doc member having the adequate expertise (as illustrated by his publications: Hepatology, oncogene, JBC, JCI) and who recently joined the group. The role of inflammasome, and especially elastases, will be investigated in the fibrotic process of the liver. This part is developed by a staff member with interest and expertise in lung fibrosis who recently joined the team. Recent data obtained in the setting of liver fibrosis have been shown during the oral presentation.

The second objective is dedicated to tumor targeting in HCC using metabolic radiotherapy with the development of radioisotopic drug delivery systems and nanoparticules. Improvement of these systems has been performed and combination with new biotherapies obtained from molecules provided by the first group will be challenged.

Scientific production demonstrates the very good level of expertise of each of the PI of the team in their respective fields (Hepatology, JCO, Oncogene, J Immunol,…).

Three patents have been obtained, 1 is pending.

National and international academic collaborations are ongoing with the main PI of the team (Finland, Brasil, Orléans & Angers in France).

21 trainees were supervised in the 5 past years (9 M2, 12 PhD).

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

The team leader and main PIs have gained an international expertise and are regularly invited in international and national meetings (2 members with 40 each). The team leader is involved in the development of the national biobank of HCC.

The constitution of the present team results from the joining of several well-known PIs having the ability to supervise trainees and attract students and post-doc. One post-doc member was recently recruited from abroad and will apply for a permanent scientific position.

Many institutional fundings (regional and national: INCA, ANR, ARC…) and industrial collaborations have been obtained.

Participation to collaborative national networks is noted.

- Appreciation on the scientific strategy and the project

The project, aiming to focus on the microenvironment of the HCC, really innovates in the field of hepatocarcinogenesis and includes both fundamental research and clinical applications in terms of diagnosis and treatment. Given the expertise of the team, the access to different platforms and the recent data obtained, the scientific project will be certainly achieved in the 4 next years. Main priorities of the project are clearly presented, even though 2 topics (Impact of Wnt signaling on the immunological environment and inflammasome) will be further developed.

The genomic approach to study HCC microenvironment is promising and will provide numbers of biomolecules potentially relevant in the pathogenesis, diagnosis and treatment of HCC.

The great capacity to obtain grants and funding will support the project.

- Conclusion :

  - Summary

Original project, based on the study of HCC microenvironment, resulting from the union of PIs of different research units and clinical departments directed by a scientist with well-recognized expertise and leadership.

  - Strengths and opportunities

The scientific objective of the project is original, partly based on data obtained by the group and new integrative genomic approaches locally available.

In vitro and human data will be analysed thanks to the access to different platforms on site

The team in that configuration is “young” and has been able to produce significant results in the past 2 years, demonstrating a very convincing global strategy

Fundamental data obtained would be further tested for clinical applications as biomarkers and biotherapies leading to an effective translational research

Leadership of the head of the team with national and international visibility.

Ability to raise funds and valorisation of data

  - Weaknesses and threats

A quite large group, possibly seeming heterogeneous, with few permanent scientists. One post-doc member, in charge of the molecular characterisation of HCC microenvironment, is applying for a permanent position. Such recruitment is essential for the achievement of a main part of the project.

One of the axis (inflammasome), initially restricted to pulmonary chronic diseases, seems to reroute towards liver diseases. This needs to be confirmed by published data. Involvement of metabolic radiotherapy also needs to be further emphasized

– Recommendations

The study of the microenvironment of HCC is really interesting and original and needs to be kept through a multidisciplinary approach that will allow a translational research activity. For that purpose, it is mandatory to focus on liver cancers and to be able to recruit permanent scientists.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
FOIE, MÉTABOLISMES, CANCER	**A**	**A**	**A+**	**A**	**A**
REMODELAGE DU MICROENVIRONNEMENT ET PROGRESSION DU CARCINOME HÉPATOCELLULAIRE [CLEMENT-CLEMENT]	A	A+	Non noté	A	A
HÉPATOTOXICITÉ DES XÉNOBIOTIQUES: MÉCANISMES ET MODULATION PAR L'OBÉSITÉ [CLEMENT-FROMENTY-ROBIN]	A	A	Non noté	A+	A
FER ET FOIE: ASPECTS PHYSIOLOGIQUES ET PATHOLOGIQUES [CLEMENT-LOREAL]	A	A	Non noté	A	A
STRESS, DÉFENSES ET RÉGÉNÉRATION [CLEMENT-MOREL]	A	A	Non noté	A	A

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	**42**	**5**	**20**	**26**	**36**	**59**	**5**	**17**	**29**	**239**
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

*** les résultats SVE2 ne sont pas définitifs au 06/05/2011.**

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

• SVE1 Biologie, santé
- **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
- **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
- **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
- **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
- **SVE1_LS5 Neurosciences**
- **SVE1_LS6 Immunologie, Infectiologie**
- **SVE1_LS7 Recherche clinique, Santé publique**

• SVE2 Ecologie, environnement
- **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
- **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
- **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

PRÉSIDENCE

Guy Cathelineau
Président

UNIVERSITÉ DE RENNES 1

Rennes, le 22 février 2011

Monsieur Pierre GLORIEUX
Directeur de la section des unités de recherche
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Monsieur le Directeur,

Je vous adresse mes remerciements pour la qualité du rapport d'évaluation fourni à l'issue de la visite du comité d'expertise concernant l'unité mixte de recherche **«Foie, métabolisme et cancer».**

L'université de Rennes 1 sera particulièrement attentive à ce que les recommandations formulées par le comité de visite soient prises en compte.

Vous trouverez ci-joint, les réponses du directeur de l'unité auxquelles le Vice-président du conseil scientifique et moi-même adhérons.

A la lecture de ce rapport, nous souhaitons apporter les précisions suivantes :

Conformément à la remarque tout à fait justifiée d'une localisation regroupant l'ensemble des équipes de recherche de cette unité, l'université de Rennes 1 souhaite engager avec ses partenaires de site (CHU, Inserm, collectivités territoriales) une planification pluriannuelle de l'usage, rénovation et construction des locaux dédiés à la recherche du secteur biologie-santé sur le campus Villejean concerné. L'unité de recherche « Foie, métabolisme et cancer » s'inscrira de manière prioritaire dans cette réflexion.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de ma considération distinguée.

Le Président de l'Université de Rennes 1

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Monsieur Pierre Glorieux
Section des unités de recherche
AERES

February 14, 2011

Sir,

We thank the members of the Review committee and the Committee chairman for their careful examination and constructive criticisms of our project unit entitled "Liver, Metabolisms and Cancer".

We really appreciated the positive comments of the committee on the overall quality of the scientific project, the global strategy, and the management of the unit. We are aware of the weaknesses and threats which were highlighted by the committee and we would like to answer to the following points:

- The committee pointed out a relatively high number of projects and the necessity to make strategic choices. We agree with this comment. Thus, to overcome this potential threat, we have decided to put our efforts on: (i) a stringent selection of projects for PhD students and post-doc fellows; (ii) the development of three transversal programs gathering projects from a minimum of two teams; (iii) application to external grants in line with the general policy of the unit. Accordingly, oral presentations during the site visit were focused on the most promising projects in each team. Furthermore, we plan to present our orientations to the Scientific Committee which will help us in defining a well focused strategy for each team.

- As mentioned by the committee, we agree that some of the data we generated may deserve publications in journals with higher impact than those where they appeared. As discussed during the site visit, our strong involvement in M2 and PhD student formation, together with the "Ecole Doctorale" rules are somewhat in contradiction with this objective and may represent a threat for a top-level policy. However, thanks to the new unit re-organization, the reduction of projects' number, the development of "at risk" and transversal projects, together with the willingness of the team leaders and staff members, we strongly believe that this goal should be rapidly achieved ;

- Demography is a main concern of the unit management. We plan to recruit young scientists in each of the 4 teams during the following years. This is indeed mandatory to add innovation and new inputs. Thus, ongoing applications include a candidate who is being applying for a CR Inserm position in team #4, a post-doc fellow coming back from the Scripps Research Institute (USA) who is applying for a MCU position in Nutrition and CR position in team #3, and a young clinician who

should apply to an Inserm "Poste d'Accueil" position in team #1. In addition, we urgently need recruiting engineers and technicians from both Inserm and the University, in order to strengthen the teams and the technical platforms which require skilled and permanent personals.

- The physical separation of the teams on two sites is a main threat which was raised by the committee. The re-localization of team #3 into a building close to the main building of the unit depends on the willingness of University which is working on a global re-organization of the Villejean campus, whereas connecting both buildings will require an agreement between the University and the Hospital. Preliminary discussions are underway, and a general architectural and financial plan will be submitted to the 3 partners very shortly, i.e. University, CHU and Inserm.

Again, we thank the members of the Review committee and the Committee chairman for their fruitful comments which will help us in re-focusing our program on the most promising and innovative projects.

Sincerely yours,

Bruno Clément
Head of the unit-991