MICA - Micro-environnement 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

MIcroenvironment and CAncer

From the

University of Rennes 1

INSERM

November 2010

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

November 2010

Research Unit

Name of the research unit: MIcroenvironment and CAncer

Requested label: UMR_S INSERM

N° in the case of renewal: 917

Name of the director: Ms Karin TARTE

Members of the review committee

Committee chairman

M Olivier HERMINE, Université Paris-Descartes, Paris

Other committee members

M Simon WAGNER, University of Leicester, UK

M Vito PISTOIA, University of Genova, Italy

M Thierry Jo MOLINA, Université Paris-Descartes, Paris

M Jean SOULIER, Université Paris-Descartes, Paris (CSS INSERM)

Ms Marie Christine BENE, University of Nancy (CNU)

Observers

AERES scientific advisor

M. Jean ROSENBAUM

University, School and Research Organization representatives

Ms Christine TUFFEREAU, INSERM

M Claude LABIT, University Rennes 1

Report

1 • Introduction

- Date and execution of the visit

The visit took place in Rennes on November 16, 2010. The site visit began at 8:30 am by a meeting of the committee with the AERES representative.

From 8:45 to 11 am, the group leader and 3 team members introduced the general strategy of the lab and the projects. The committee then split into 3 subgroups in order to meet separately the PhD students, the techicians, and the scientists. The committe then met University, INSERM and other local representatives during 30 minutes.

At 1 :00 pm, the committee met for debriefing and drafting the report. The visit ended at 3 :00 pm.

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

The team as such was created as a monothematic INSERM Unit in 2008. It is located in a building of the University of Rennes, close to Rennes University Hospital. It is a small team, highly focused on the understanding of the role of the bone marrow and lymph node microenvironments in B cell lymphomagenesis.

- Management team

This small team is directly managed by its director.

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	6	6
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	6	6
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)	4	
N7: Number of staff members with a HDR or a similar grade	6	6

2 • Overall appreciation on the research unit

- Summary

This is a young team that is well integrated in the context of the university hospital of Rennes. This team focuses its work on the pathophysiology of B cell lymphoproliferative disorders with a focus on the role of the stromal niche on B cell growth. The team is headed by a very charismatic director, an immunologist who is working in close collaboration with both the university departments of clinical and biological hematology. As a result of these collaborations they have built a strong structure, almost unique in France, involved in basic and translational research on B cell lymphoproliferation that will certainly develop in the future. However, an effort should be made to increase their research on more basic aspects of the normal B cell development and pathophysiology of B cell transformation to develop new hypotheses that they could confirm in human diseases. They have the capacity to integrate new teams of young promising scientists because of the high potential of their field of research, the intellectual potential of the leaders of this unit, the good scientific environment, the ability to work on human samples, and the space availability and good core facility. Actually, in this respect they have recently recruited a new young scientist who has identified new genes involved in B cell development that may play a role in B cell transformation. Hopefully with the reinforcement of this new scientist and others they will be able to publish good work in generalist journals with a higher impact factor than the best hematology journals in which they are already currently publishing.

- Strenghts and opportunities

This monothematic team focuses most of its efforts in trying to understand the role of the microenvironment on the development of B cell neoplasia. This topic of research is ambitious and this team is one of the international leaders in this field. They are well connected with European Networks. They have built a very strong and impressive network between the clinical hematological department, biological hematological department and their INSERM unit. This network extends to regional hematology centres that provide them with good quality samples for diagnosis and research. The leaders of these three structures are working well and synergistically together. As a result they benefit from a large number of patients samples that they can use for research purposes. From their work they have the capacity to go from the bench to the bedside and vice et versa. In the near future they will develop phase 1,2 studies based on their scientific works. The leader of this team has a very good scientific background and is well known in France as well as outside. The laboratory is very well organized in a very nice environment, with a good quality of work and complies with every regulatory aspect. No conflicts have been evidenced between students, technicians, researchers, and team leaders. This unit is supported by both the university and the hospital and is well integrated in both structures. In addition they have obtained a strong financial support from the city and they have been able to get funding from ANR, Ligue contre le cancer, Association contre le cancer, etc. They have a strong potential to grow up and to recruit new teams to develop more fundamental aspects of B cell lymphomagenesis and to promote researchers from inside to get a tenure positions either within an EPST or at the university. In this regard they recently recruited from inside a new CR1.

- Weaknesses and threats

The main weakness of this unit is the low number of basic scientists that could bring more insight to the molecular and cellular mechanisms of lymphomagenesis. For example, they should develop more basic aspects of apoptosis for some aspects of their work.

Probably partly as a consequence of this low number of basic scientists, they have not been able to publish in general journals with high impact factors.

In addition, most of their students and post docs have not yet published their work and do not communicate sufficiently outside their laboratory within the campus nor in national and international meetings.

- Recommendations

The unit should maintain the same pathway of research. However, it is strongly recommended to try to recruit new researchers in order to exploit the full potential of their field of research now that they have built strong basis to do so. Particularly they should develop some basic aspects of their research to improve their number and level of publications.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	6
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	1
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	5

3 • Specific comments

- Appreciation on the results

The team has obtained significant findings in its different thematic axes. They demonstrated the role of the mesenchymal stromal niche in B-cell lymphoma pathophysiology. They were also able to generate clinical-grade human mesenchymal stem cells.

Since its creation, the team has published 23 publications strictly derived from their own research program, among them 12 with an impact factor above 5. This includes notably 2 publications in Blood (IF> 10), and others in Cancer Research, Leukemia, Oncogene, Journal of Immunology. They also published 22 articles as collaborative work and an additional 18 clinical publications. Given the low number of scientists, this is an excellent achievement.

Five PhD theses have been defended.

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

The team has an excellent national and international recognition. The team leader has been invited 10 times to give talks in meetings.

They have recently succeeded in attracting a young scientist to the lab, who was then recruited as an INSERM scientist, which indicates their attractiveness.

The unit has made a good effort to try to valorize their work by the deposition of patents. In addition, they have succeeded in connecting their work with the clinical investigation center, to develop new prognosis tools and new therapeutic strategies of B cell lymphoproliferation.

They have obtained a strong financial support from the city and they have been able to get competitive funding from the FP7 program (they are partners in two networks), ANR, Ligue contre le cancer, Association contre le cancer, etc. They have also obtained good research grants from biotechnologies and pharmaceutical companies.

In addition they have set-up collaborative work with the laboratory of the Etablissement francais du sang to develop new antibodies and to optimize the use of mesenchymal cells as immunosuppressive cells that they will try to valorize through collaborations with private companies.

- Appreciation on the management and life of the research unit

There are very good management and life in the research unit. A great organization in all aspects of regulation has been set-up.

The governance is well carried out with a strong and efficient collaboration between researchers and MDs. Members of the unit who are MD/PhD combine working both within the unit and with clinical and laboratory duties. They should push more their students and post docs to focus on their works to get publications and to communicate more outside the lab.

The members of the unit have a strong involvement in teaching activities in M2 and PhD schools, and medical university. In addition they have organized national and international workshops.

- Appreciation on the scientific strategy and the project

Taken together the strategy of the project is clear. The team is and will remain focused on specific aspects of B cell lymphomagenesis, and they will try to develop more basic research within this field of research that may serve in the future to develop new prognosis markers, and treatments of lymphoma particularly targeting the microenvironment.

The project is overall a good project, with a sound design of their goals and experiments in the near future. The leader of the unit and her collaborators know where they are going and they know how to reach their goals. However, they should put more emphasize on deliverables, particularly on publications.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
MICRO-ENVIRONNEMENT ET CANCER - MICA	A	A+	A+	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 8 avril 2011

Vos réf. : S2UR120001338
MICA– 0350936C

Monsieur Pierre GLORIEUX
Directeur de la section des unités de recherche
Agence d'Evaluation de la recherche et de l'Enseignement Supérieur (AERES)
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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 **«Micro-environnement et Cancer (MICA)** ».

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

A la lecture de ce rapport, vous trouverez ci-joint, les réponses du directeur d'unité auxquelles nous souscrivons en totalité, en y ajoutant quelques précisions sur les trois éléments suivants :

L'unité de recherche « Micro-environnement et Cancer », associée à l'Inserm, développe avec un grand dynamisme une recherche en lien étroit avec le secteur clinique et s'inscrit ainsi dans le partenariat stratégique de recherche que l'université de Rennes 1 souhaite entretenir avec le CHU de Rennes.

Cette jeune équipe poursuit des travaux scientifiques reconnus et focalisés sur une thématique précise et d'envergure, et à ce titre, se doit d'être confortée à l'avenir par l'intégration complémentaire de ressources humaines et financières.

Enfin, l'unité de recherche « MICA » s'inscrit fortement dans l'animation collective du secteur Biologie-Santé de l'université de Rennes 1. Elle est en particulier impliquée au sein de la structure fédérative de recherche « Fédération de recherche en biologie et santé de Rennes ». Cet outil qui mutualise les plates-formes scientifiques du domaine Bio-Santé, est indispensable pour le renforcement de l'animation et de la coopération inter-unités au sein de ce secteur de recherche de l'université de Rennes 1.

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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RESPONSE TO AERES COMMENTS

We thank the committee for its overall positive evaluation and for its appreciation of our team as a "*strong structure, almost unique in France, involved in basic and translational research on B cell lymphoproliferation that will certainly develop in the future*". Our response is based on the weaknesses pointed out in the report and the related recommendations made by the committee that will be helpful to develop the full potential of our projects.

Weakness 1/Recommendation 1: Low number of basic scientists/Try to recruit new researchers

As highlighted in our internal SWOT analysis, we fully agree with this comment and have made a strong effort in the past 2 years to recruit a young CR1 and provide him with adequate starting conditions in order to develop his own project on the role of ING1/ING2 genes in normal and malignant B cell biology. In addition, whereas our team included only one post-doc until now, two new post-doc were recruited in the past three months. Of course, one of our priorities will be to attract other basic scientists with complementary expertise to further develop our core research program. In addition, since we have fully-equipped free lab space and a strong clinical network including a unique tissue bank, we could also welcome a new research group, for example an ATIP/Avenir team, developing a closely related but independent research program using state-of-the-art mouse models and/or molecular tools. This will guarantee the continuity and the development of our whole unit and reinforce our capacity to reach scientific and technical breakthroughs.

Weakness 2/Recommendation 2: They should develop some basic aspects to (be) able to publish in general journal with high impact factors

Overall, we regret that the evaluation committee did not provide a more in-depth analysis of our scientific achievement and project. However, we agree that whereas our "*project is overall a good project, with a sound design of goals and experiments in the near future*" we have identified some scientific priorities that will give rise, in the mid-term, to high-rank publications and put joined efforts on these specific topics.

- WP1. Normal and malignant GC-derived B-cell differentiation.

Based on our preliminary data, we think that two main aspects should be particularly focused on.

× First, our original model of *in vitro* naïve B cell differentiation allows us to ask important basic questions on normal and malignant B-cell behavior. In particular, we have identified a STAT5-dependent transcriptional pathway that is crucial for the mature B-cell differentiation process and is under investigation. Importantly STAT5 expression and activation are upregulated in

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GC-derived B cell lymphomas. In addition, we are currently focusing our work on the $CD20^{pos}CD38^{pos}$ subpopulation that is actively cycling, overexpress AID at high level, and is prone to apoptosis. Our hypothesis is that these cells could accumulate DNA-damage and genomic instability in the presence of anti-apoptotic stimuli, and we plan to test it both *in vitro* and *in vivo.*

× Second, the ING1/ING2 program has been identified 2 years ago as a new and promising project and will be further supported in the future. We have obtained specific funding from EFS to get the ING1 KO and ING2 KO mouse models and will receive them soon. We have identified for the first time the role of ING genes in DNA repair and have developed the tools to further study at the molecular level their implication in class-switch recombination and lymphomagenesis. This project gathers both a highly specific mechanistic approach and relevant *in vitro* and *in vivo* biological models. In addition, ING1 KO mice have been shown to develop spontaneous FL-like lymphoma and FL mouse model will be a major original tool for the study of both B cell and stromal cell alterations during lymphomagenesis.

- *WP2. GC-derived B-cell niche*

In the past few years we have generated a huge amount of phenotypic and transcriptomic data on the different cell subsets of lymphoma microenvironment. We develop now scientific approaches to go deeper into the understanding of the mechanisms of the observed alterations. In addition, we have recently developed new tools, in particular based on multicolor microscopy on human tissue slices, which allow us to evaluate the relevance of our results *in vivo* within the tumor.

× First, concerning the stromal part of the project, we are focusing on the transcriptional pathways that we found deregulated during interaction between malignant B cells and normal stromal cells and try to decipher how they could redirect stromal cell differentiation into B-cell supportive lymphoid-like phenotype. In addition, we will continue the characterization of stromal cell heterogeneity *in vivo*, in the bone marrow and lymph node niches, a crucial step to validate our concepts. We have developed adequate microscopy and flow cytometry/cell sorting strategies that allowed us, owing to our unique tissue collection, to propose for the first time a phenotypic and functional definition of stromal cell niche in human. This last part of the project is the basis of our collaboration with several partners involved in the same field in mouse models.

× Second, concerning the T_{FH} project, we have already included in our work a more basic project in collaboration with Nicolas Fazilleau (INCa Libre 2010). In fact, our recent data on T_{FH} characterization in FL have highlighted the combined deregulation of a set of genes involved in T-cell polarization that will be tested *in vitro* but also *in vivo* in the mouse models developed by our collaborator and by our team, for their role in the acquisition of a FL T_{FH} phenotype and function.

We hope that, in addition to the projects that are currently under realization and, for some of them, are submitted for publication, these specific goals could provide us with fully original and interesting data that could be transformed into high-level publications. We just would like to emphasize that one of our main originality is to integrate B cells together with their complex microenvironment within human lymphoma niches. As discussed by the committee, we think that this approach is the only way to "*develop new prognosis tools and new therapeutic strategies of B cell lymphoproliferation*".

Weakness 3: Most of their students and post-doc have not yet published their work and do not communicate sufficiently outside their laboratory

This specific points should be discussed as some elements have perhaps not been enough underlined. As indicated by the committee, five PhD theses have been defended in the past 4

years. All these students have published their results as first authors in good to very good journals as followed: i) HMEJ: 1 Blood 2007, 1 Cancer Res 2009 (currently post-doc fellow in Switzerland); ii) MT: 1 JI 2009 (currently post-doc fellow in Creteil); .iii) GN: 1 Hum Immunol 2008, 1 Clin Immunol 2008, 1 Int Immunol 2009 (currently post-doc fellow in Canada); iv) DM: 1 J Infect Dis 2010 (MD PhD, currently PH in Immunology in Rennes hospital); v) SLG: 1 JI 2009 (currently post-doc fellow in Paris). In addition, all of them have presented their work in international or national meetings even if we agree that, due to budget constraint, most of them only participate to meeting in France. The PhD student that will defend his thesis this year has one manuscript under review and a second one in preparation and has already presented his work 4 times outside Rennes (5th International conference on tumor microenvironment, SFH, B-cell workshop in Oleron, Colloque cytokines du Croisic). Nevertheless, participation to international meeting will be encouraged with a potential financial contribution of the unit for the support of PhD students and post-doc fellow.

Rennes, April 15th, 2011

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