LAMC - Laboratoire de l'angiogenèse et du microenvironnement des cancers

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Molecular Angiogenesis Laboratory

From the

University Bordeaux 1

INSERM

May 2010

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INSERM

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

May 2010

Research Unit

Name of the research unit : Molecular Angiogenesis Laboratory

Requested label : UMR_S INSERM

N° in the case of renewal : U920

Name of the director : Mr Andréas BIKFALVI

Members of the review committee

Chairperson :

Mr Fabrice SONCIN

Reviewers :

Mr David O. BATES, University of Bristol, United Kingdom

Mr Erhard HOFER, Medical University of Vienna, Austria

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

Mr Eric RUBISTEIN, CSS INSERM representative

Mr Olivier OUDAR, CNU representative

Representatives present during the visit

AERES scientific advisor:

Mme Marie-Annick BUENDIA

University or School representatives

Mr Alain BOUDOU, Président Université Bordeaux I

Mr Jean-Pierre RENAUDIN, Directeur UFR de Biologie

Mr Alain RAVAUD, représentant l'axe Cancer du CIC

Mr Nicolas MOORE, Directeur du CIC-P, du CHU de Bordreaux

Mme Lucie BESSE, représentante de l'ADR9 de l'INSERM

Mr Jean ROSENBAUM, directeur de l'IFR66

Research Organization representatives

Mme Chantal LASSERRE, chargée de mission CSS2 INSERM

Report

1 • Introduction

- Date and execution of the visit

The visit took place on November 24th, 2009. After a brief closed-door gathering of the visiting committee, the laboratory director made a general presentation of the team's main achievements and its activities within the Bordeaux research and clinical networks. Each group leader then presented its past results and projects and answered committee members' questions. The committee met with representatives from Bordeaux I University, IFR, UFR, hospital and INSERM which all showed strong support of the activities of the team. The committee then heard separately the students and post-docs, the scientists, and the technical staff. The visit was concluded by a 3h30 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 Andréas Bikfalvi in 1996 as a University laboratory, then as a CNRS FRE for one year (1999). It became an INSERM unit (E113) in 2000, which was renewed as an INSERM single-team unit in 2006 (U920). It averages a total of 20 people and is localized on the University of Bordeaux I campus in Pessac, on 691 m2 on the ground floor of the Bâtiment de Biologie Animale which has been renovated recently. The laboratory is fully equipped for molecular and cell biology and has access to a full scale animal facility (next building) equipped with in vivo imaging equipment. Other available core facilities include genomic, lentivirus, and electron microscopy facilities. Other core facilities are accessible through the Cancéropole Grand-Sud-Ouest. The laboratory is working on the general field of angiogenesis, the formation of new blood vessels. It is particularly focused on tumour angiogenesis and, in the recent years, has setup several new tools for identifying and studying new genes involved in this process.

- Management team

The team is headed by Andréas Bikfalvi and subdivided into three research groups corresponding to the 'Stress and angiogenesis', 'Models of tumour angiogenesis in vivo' and 'stimulators and inhibitors of angiogenesis'

- 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	7
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)	5	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	4
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	3	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	4
N7: Number of staff members with a HDR or a similar grade	5	6

2 • Overall appreciation on the research unit

• Overall opinion

This Unit is an innovative, original and cohesive research team that continues to push the boundaries of current angiogenesis research both at the academic and technical levels. It is seeking to expand its translational activities by exploring original therapeutic targets and forging appropriate connections within local clinical and national scientific arenas. Their focus on ensuring applicability to their finding through patent generation is laudable but it is also important that they cement the impact of these findings by defining the mechanisms through which these discoveries exert their effects.

• Strengths and opportunities

- Setup of original genomic applications on tumour models on the chicken CAM and use of several orthotopic tumour models in mice;
- Interesting and potentially valuable applications of previously unlinked proteins to anti-angiogenic activities (CXCL4L1, Kinesins);
- Novel area in the unfolded protein response as contribution to angiogenic research (IRE1);
- Good collaborative projects and insertion in the national network;
- Good insertion in the local translational network;
- Translation from bench to bedside;
- Ability to raise funds through competitive grant applications;
- Quite young group leaders;
- Intellectual property protection ;
- The good cohesion and spirit of the team.

• Weaknesses

- Mechanistic approaches not sufficient;
- No clear description of strategic goals defining the interesting targets among the newly found genes;
- Strategy for bench to bedside translation is not sufficiently defined;
- Output is generally lacking high profile journals;
- Allocation of resources and workplan underdeveloped;
- Career progress for intermediate research staff not clear;
- No indication of the career progression of the previous students and post-docs;

• Threats

- The lack of expertise in transgenic mice.

• Recommendations to the head of the research unit

- The Director should seek to improve the impact of the novel and innovative research by investigating the mechanisms underpinning these findings in details;
- The lack of a full time research scientist was noted during the visit, the Director should be encouraged to secure recruitment of high profile post-docs that would be able to apply for INSERM or CNRS permanent position.

- Data on the work produced

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	7
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	0
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	2
A5: Number of PhD granted during the past 4 years	6

3 • Specific comments on the research unit

- Appreciation on the results

Relevance and originality of the research, quality and impact of the results: One of the most original aspects developed by this team is the application of differential transcriptomic analyses of stroma (chicken) versus cancer (human) of xenografts on the chick chorioallantoid membrane (CAM). Using different cancer models (human glioma, pancreatic and kidney cancer), this approach has allowed the team to identify several genes that are differentially regulated either in the host (endothelial and other stromal) cells during tumour angiogenesis or in the cancer cells during tumour progression. The identification of novel angiogenic modulating properties of CXCL4L1 and the novel findings in terms of IRE1 are other key findings that will progress the field on terms of antiangiogenics.

Project 1: New targets and mechanisms: This group is efficiently headed by two researchers with teaching duties. Over the past few years, the group has setup human tumour xenograft/chicken CAM models and used genomic approaches to identify several genes regulated during glioma, pancreatic and renal tumour angiogenesis, but also during normal embryonic development, and VEGF-induced angiogenesis. Studies have generated a large number of potential targets as well as several articles based on the setup of these models, the effects of anti-VEGF or of combined anti-VEGF/IL-6 treatments and the validation of target genes in glioblastoma (FBXW7/hCDC4, parvin). More recently, it has characterized several kinesins that are induced in response to VEGF. This constitutes the bases for the proposed research projects.

Project 2: Stimulators and inhibitors of angiogenesis: This group has worked for several years on CXCL4 and has recently discovered that a new variant of this chemokine, named CXCL4L1, is much more active as an antiangiogenic molecule in vitro and in vivo than CXCL4 and displays different biophysical properties (biodisponibility, binding to glycosaminoglycans, etc). They have also identified various mutants of CXCL4 that are more active. The committee appreciated that this group chose to conclude the studies on FGF dimerization and LYVE-1 interactions, and the studies on in vivo biotinylation and proteomics to focus on the more novel studies.

Project 3: Stress and angiogenesis: This group has identified a role of IRE1 in the regulation of tumour growth and angiogenesis (glioma). The development of the dominant-negative approach (DN) was successful and is still valuable. Further, the confirmation of a role of amifostine in angiogenesis inhibition should enable the group to go on and further explore the role of the unfolded protein response in the angiogenic process. The various findings from all the groups will have a significant impact on the research field of angiogenesis. This is an important step toward their next major challenge: to have a significant impact on healthcare.

The laboratory has published 31 original articles since 2005, among which approximately one third originated directly from the team's subjects (articles where team members signed first and last authors), indicating that the team has a lot of productive collaborations. Major articles include:

- A paper in PNAS 2005 on the setup of the tumor model on the CAM;
- Two papers in Cancer Res 2007 on the role of IRE1 in angiogenesis and on skin-derived stem cells in brain tumor animal models ;

- A paper in J Cell Physiol 2007 on VEGF expression in human carcinoma cells under glucose deprivation;
- A paper in Blood 2007 on the localization and secretion of the PF-4/CXCL4 and CXCL4L1 chemokines;
- A paper in PLoS One 2008 on the role of CXCL4 in angiogenesis;
- A paper in Int J Canc 2008 on the identification of genes regulated in glioma;
- A paper in Int J Canc 2009 on the targeting of IL-6 together with VEGF on glioma.

In addition, the team has filed 5 patents during the past contract. The team, taken by itself and with its collaborators, has a very good output combining patents and papers. However, given the tools, the novelty and originality of the findings, the primary publications of this team could have been in higher profile journals if the mechanistic links had been described. The director of the Unit has been invited to talk in approximately 30 national and international conferences since 2005. He has been co-organizer of a major international angiogenesis meeting series from 1999 to 2009. However, aside from his participation in this series, he has only three high-profile invitations over the past period (ESMO, NCRI, AUA). Of note, two of the groups have had selected talks from abstracts.

Although there are currently no partnerships corresponding to the filed patents, it will be important over the next period to develop commercial or industrial links to realize the value of these patents.

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

The lab has excellent links with international groups in the field, particularly productive with groups in Milan and Montreal. There have been a number of excellent collaborations within France, particularly based on the cancer CAM model, which have gone some way to enhancing French's angiogenesis research profile. There is a very strong support and commitment from the local university and hospital authorities and an expectation to develop translational research from this laboratory into clinical research, in particular through the cancer axis of the CIC.

The team recruited 4 international post-docs, from Uppsala, Berlin, Milan (2) and 4 ERASMUS students during the last contract, received 3 visiting scientists from Italy and Germany on a regular basis, although none of these have gone on to secure personal support in the team. The team leader has convinced the Hospital and University to recruit a high-profile Professor in this field of research with a specific role to complement this team and strengthen translational research.

The team participated to two 6th FPU European projects (STROMA, ARGES), obtained or participated to 7 ARC grants, obtained 5 Ligue Nationale contre le Cancer grants, coordinated 3 ANR grants and participated to one ANR program (one ANR program for transfer 2008-2009), obtained one and participated to 4 InCA programs. Combined with post-doc and student fellowships that are not mentioned in the present AERES report, this has resulted in the creation of a substantial and self-sufficient research unit.

The team has deposited 5 patent applications since 2004 : MMP-2 peptides, Aminothiol compounds, PF4V1, CXCL4 mutant, CXCL4 as a pancreatic cancer marker.

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

The team is well organized and structured in three groups with independent projects and which share tools and competences. They have clearly defined responsibilities and appear very cohesive. The team organizes bi-weekly meetings and journal clubs to share results and comment on general lab organization problems and progress. The persons in charge of progress sign as last authors on their own group papers. In the absence of an INSERM or CNRS research scientist, the groups are run by teacher-researchers with substantial teaching charges.

The team should define a clearer strategy for deciding which target they choose to develop among the many genes that they have identified through their various screens.

All permanent researchers of the team are teacher-researchers at the University, thus implying a 50%-time involvement in teaching.

- Appreciation on the project

Project 1: New targets and mechanisms: This group has spent an extensive amount of effort recently to come up with several candidate genes markers of tumour angiogenesis or of tumour progression in human. It proposes now to focus its work on the role of kinesins in VEGF-induced angiogenesis. From the different genes identified so far, the focus for future studies has been put on kinesins mainly because of rapid potential therapeutic applications. The choice of which target to develop further thus appears to be based on existing therapeutics and the process through which additional targets will be followed up could be better defined. The committee recommends that a clear development pathway is implemented so that their findings can be translated into clinical practice within a reasonable time frame, ideally, during the next contract. Further, their strategy to translate this to clinical trials should be identified.

Project 2: Stimulators and inhibitors of angiogenesis: The project focuses on determining the effects of the chemokines on different cell types in vitro and in vivo, and on describing their pattern of expression in physiological and cancer situations, as well as evaluating its potential as a biomarker. The project does not clearly address how the mechanism of actions of these molecules will be investigated as opposed to just what their actions are. The fact that the CXCL4L1 gene is not present in mouse limits the genetic manipulation approaches and emphasizes the value of collaborating with groups working on primate models. However, genetic overexpression (knock-in) and K14-transgenics studies will yield valuable results, particularly if combined with inducible promoters. The translational project evaluating the value of chemokine levels in clear cell renal carcinoma patients is interesting but the relevance to how the findings may affect patient's care should be considered (see comments on translational strategy).

Project 3: Stress and angiogenesis: The project proposes to identify the mechanisms by which IRE1 kinase and RNase activities participate to the regulation of angiogenesis by the use of various deletion mutants. While it explains clearly how they will modify the IRE1 and its immediate downstream targets, it is not clear how this relates to angiogenesis per se, e.g., endothelial cell behaviour.

The projects vary in their scope from relatively focussed intermediate term research projects (e.g. IRE1) to a wide ranging longer term development plan (e.g. CXCL4L1). Three pathways prevously identified in the various models will be analyzed in more details during short to medium range projects. Preclinical resuts of the relevance of the targets/pathways should be obtained in the medium term and any of the targets/pathways identified as important in the preclinical models should provide long-term perspectives for bench to bedside translation. The projects' relevance and feasibility are reasonable if continued research support is forthcoming. Given the groups' history of successful grant applications, successful results from the research projects appears to be likely.

The team has previously setup original approaches to question tumor angiogenesis and how to target it, both at the technical and conceptual level. The current proposal is based on selected, some novel and original potential targets identified in the previous contract, stressing the ability of the different groups to follow risky approaches. The team has a good balance of highly original, relatively risky projects (e.g. Kinesins), unearthing of neglected but previously discovered research areas (amifostine, CXCL4), and application of low risk, high feasibility studies (VEGF/IL6).

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

We would like to respond herein to the commentaries of the evaluation committee. Our impression from the commentaries is that the evaluation was overall positive. We clarify below some of the issues the evaluation committee raised in its report:

Point 1: Additional information on mechanistical approaches

We have, in the past, explored mechanistical aspects of several genes and proteins. For example, we demonstrated that endogenous FGFs modulate glioma development by both angiogenesis-dependent and independent mechanisms (**P. Auguste *et al.*, *Cancer research* 61, 1717 (Feb 15, 2001)**). We have also demonstrated that CXCL4 associates directly with Fibroblast growth factors and inhibits their dimerization and receptor activation(**C. Perollet, Z. C. Han, C. Savona, J. P. Caen, A. Bikfalvi, *Blood* 91, 3289 (1998)**); (**R. M. Lozano *et al.*, *The Journal of biological chemistry* 276, 35723 (2001)**), or with integrins (**S. Aidoudi, K. Bujakowska, N. Kieffer, A. Bikfalvi, *PLoS One* 3, e2657 (2008)**). We had also identified the interacting domain with the growth factor (**L. Ragona, S. Tomaselli, C. Quemener, L. Zetta, A. Bikfalvi, *Biochemical and biophysical research communications* 382, 26 (Apr 24, 2009)**). As for the new form, CXCL4L1, we have made mechanistical observation with regard to its interaction with glycosaminoglycans and biological activity (Dubrac et al., submitted). We have also established a role for endogenous CXCL4L1 in the control of pancreatic tumorgenesis (Quemener et al., in preparation). Another example is IRE1, a kinase involved in the unfolded protein response (UPR). IRE1 signalling depend on both, its kinase and RNase activities. Several mutations in the two *IRE1/ERN* genes isoforms have been reported in different types of tumors including glioblastoma (**I. C. Greenman, E. Gomez, C. E. Moore, T. P. Herbert, *J Endocrinol* 192, 179 (Jan, 2007)**). Using site-directed mutagenesis and deletions, we are caracterizing the respective contribution of the two catalytic (kinase/RNase) domains on the phenotype of malignant gliomas. We furthermore elucidated the mechanisms of action of amifostine, a drug used in cancer patients, in tumor development (Dedieu et al, BMC Medecine, accepted MS).

It is of course our intention for the next contract to increase the effort with regard to the mechanistical aspects of our research.

Point 2: Description of strategic goals defining the interesting targets among the newly found genes

In our transcriptomic analysis we can distinguish three classes of genes of interest: 1) Unknown genes, 2) Known genes of unknown function, 3) Known genes with known function but not known to be involved in tumor angiogenesis or invasion.

Our filtering criteria are based on the following additional information: Over-expression or under-expression of a regulated gene in human cancers (Oncomine database and qPCRs), transcript enrichment in endothelium (*in silico* prediction using bioinformatic methods), Literature mining (PubMed), classical fold-change (e.g. focus on genes with more than 2-fold change), transcript abundance and state-of-the-art statistical tests. All these informations together contribute therefore to the decision to further study a gene or not.

This is followed by knock-down of candidate genes in endothelial cells. This strategy was applied, for example, to parvins or endothelial kinesins.

Point 3: Additional information on the strategy for bench to bedside translation

Different strategies for translations into the clinic are developed in the laboratory. These include 1/ Validation of targets identified in experimental studies in patients, 2/ Patenting of inventions for further clinical development, 3/ Preclinical validation of novel therapeutic strategies and translation into the clinic. Thus, our strategy involves close interaction with clinical centres, and we also aim to set up-a start-up for the development of our patents on chemokines.

We were/are focussing on three tumor types.

1. Glioblastoma

As mentioned in our project, IL6 is a potential molecule that we evaluate in combination with VEGF inhibitors in preclinical settings. Preliminary results suggest that the combined administration of Avastin (anti-VEGF) and Actemra (anti IL-6R) significantly reduces tumor growth and invasion, a feature that is dramatically induced by Avastin alone in glioma patients. As mentioned during the visit, we now seek to engage in a project together with 2 clinical teams, lead by P Verrelle (CHU Clermont-Ferrand) and O Chinot (CHU Marseille). We will validate combinatorial therapy in the clinical setting on a cohort of patients with recently archived GBM biopsies. We will also complete this with pre-clinical studies.

As aforementioned, single mutations in *IRE1* gene isoforms were detected in human cancers and IRE1 was proposed as a major contributor to tumor progression among protein kinases (**C. Greenman *et al.*, *Nature* 446, 153 (Mar 8, 2007)**). In collaboration with P Vajkoczy (Dept of Neurosurgery, La Charité, Berlin, Germany) we aim to check *in situ* the efficiency of IRE1-dependent RNase activity in both human glioblastomas and gliosarcomas. Tumors exhibiting an inactivated form of IRE1 will be further analyzed in order to determine the mutation(s) leading to IRE1 inactivation. In the second study (collaboration E Chevet Inserm U889, Dir. J Rosenbaum and C Di Meglio, Inserm U869, Dir. J-J Toulmé), the identification of structured oligonucleotides (aptamers) inhibiting IRE1/XBP1 signaling will be performed. These ligands will be identified through rational (decoy) and combinatorial approaches (aptamers).

2. Renal Cell Carcinoma

We have established a close interaction with the CHU Bordeaux on this project (department of clinical oncology, A Ravaud; department of urology, JM Ferrière, Geneviève Chêne, l'Institut de Santé Publique, d'Épidémiologie et de Développement, ISPED). Our laboratory is now part of the theme «Tumor Angiogenesis » of the Center for Clinical Investigation (CIC-P). We are currently analyzing in a retrospective and prospective study the role of CXCL4L1 chemokine and receptors as a biomarker for ccRCC. Preliminary data indicate that expression of CXCL4L1 is negatively correlated with tumor progression. We will also collaborate with JJ Patard (CHU Rennes) for increasing patient numbers.

3. Pancreatic carcinoma

We have established an interaction with the department of visceral surgery of the university of Saarbrück, Germany (Head : Pr M Schilling). We have established that Netrin-1 (**L. Dumartin *et al.*, *Gastroenterology*, (Jan 18, 2010)**) and CXCL4L1 (Quemener et al., to be submitted) are significantly overexpressed during tumor progression and in tumor samples from patients. While we are not pursuing Netrin-1 (because of already existing patents for this molecule in cancer), we have patented CXCL4L1 as a biomarker for pancreatic ductal carcinoma. We aim now, similar to ccRCC, organize collaborations with clinical centres to validate CXCL4L1 as biomarker in pancreatic adenocarcinoma.

Point 4: Impact of publications

The unit has published in the past regularly in journals such as Cancer Research (IF 7.5) and Blood (IF 10.4). It is more difficult for clinically-oriented experimental cancer research to publish in Nature, Cell or Science. Furthermore, the history of the team and its size and the lack of full-time permanent researchers may also account for lack of high impact publications. However, we had 1 paper published in PNAS in 2005 (IF 9.38), and 1 paper from the laboratory is now in revision in « PNAS » (UPR project). One paper has also been accepted in Gastroenterology in January (IF 12.6). While another paper on the chemokine project is under consideration in « Blood », a second paper on this project is being submitted to PlosMedecine (IF 12.2) in the forthcoming weeks. Thus, we expect very soon to increase the number of publications in high impact factor journals.

Point 5: Allocation of resources and workplan

Two tables in the application (report file, page 6-7; project file, page 14) depict the resources obtained by the laboratory for the different projects. While most of the funding is obtained by the director of the Team, every group must contribute and obtain additional funding for the specific projects, in order to be eligible for senior authorship on the papers.

Point 6: Career progress for intermediate research staff

We want to give herein some additional information on the career progress of intermediate research staff.

The majority of the intermediate research staff obtained a promotion. Career development within the same position is difficult in France and promotion is often only possible when people move to another research unit or university. However, in our laboratory, career development is facilitated by the fact that these agents are working in a competitive and stimulating environment and because they are associated with publications of the research unit. This is illustrated by the following examples:

Xavier Canron was a technician and was associated with 10 publications. He obtained a promotion as an Engineer and has moved to the department « hygiene et sécurité » of the university.

Raphaël Pineau was a technician (Adt) in the laboratory. We initiated the building of a new animal facility in 2004 and promoted his recruitment as the head of this facility. He has been associated to 2 publications.

Nathalie Courtois was a technician (Adt). She was associated to 3 publications and was promoted to a superior technician position (Tech).

Géraldine Miquel was recruited on a contract on a technician position. She obtained a permanent position in the laboratory as a superior technician (« assistant Ingénieur »).

Point 7: Career progression of the previous students and post-docs

Master students from the laboratory either pursued their career by a PhD thesis or were seeking employment for a technician position. PhD students generally pursue their career abroad by a post-doctorate. This is generally the case for our laboratory. However, some of the students seek immediately employment (Superior technician-Engineer position) or use their background to get further training in other areas such as scientific project management. A number of post-doctoral fellows went on for another post-doctoral employment, while others obtained a permanent position (University etc.).

Point 8: Information on expertise in transgenic mice

The Unit has previously proven expertise in the design, breeding and analysis of transgenic mice. Before being recruited in the laboratory, S Javerzat had actively

participated in the creation of Bordeaux's transgenic facility. Mice expressing dominant-negative form of FGF receptors under different promoter controls were the first transgenic lines produced in Bordeaux by our team (**B. Rousseau *et al.*, *Experimental eye research* 71, 395 (Oct, 2000) ; B. Rousseau, F. Larrieu-Lahargue, A. Bikfalvi, S. Javerzat, *Experimental eye research* 77, 147 (Aug, 2003) ; B. Rousseau *et al.*, *Cancer research* 64, 2490 (Apr 1, 2004)**). We have furthermore obtained transgenic or knock-out lines from other laboratories necessary for our projects (PF4 -/- mice, A Kowalska, University of Pennsylvania; mice with the conditionial VEGF null allele, N Ferrara, Genentech; Rosa VEGF 165 mice, A Nagy, Lunenfeld Research Institute, Toronto).

Interfering with angiogenesis in the mouse is delicate as it often results in embryonic lethality. For this reason, over the last 4 years, the unit has developed alternative models such as the chick embryo model and also uses the zebrafish for gene function exploration. In the near future we still plan to design and study more mouse mutants. We are currently evaluating the feasibility of new project that could start as early as beginning of 2011. Minos BioSystems (UK) has just released a mouse genetrap transposition system that generates random mutations (**T. de Wit *et al.*, *Molecular and cellular biology* 30, 68 (Jan, 2010)**) which can be directly screened on an endothelial specific GFP expression background. We have all the necessary tools to carry-out this project (mouse space as well as all bioimaging equipment).

Point 9: Recommendations to the head of the research unit: *The Director should seek to improve the impact of the novel and innovative research by investigating the mechanisms underpinning these findings in details;The lack of a full time research scientist was noted during the visit, the Director should be encouraged to secure recruitment of high profile post-docs that would be able to apply for INSERM or CNRS permanent position.*

As detailed in the previous sections, our laboratory is now significantly increasing its effort on the mechanistical aspects.

Furthermore, with respect to recruitment, a full-time INSERM scientist will join the laboratory at the end of the year to establish a second team in the unit. Support from the university and the Aquitaine Region is under negociation.

Recruitment for a permanent position at INSERM is very difficult. We had presented in 2008 a candidate with a top-ranked publication record for a permanent position at INSERM (CR1). This candidate was preselected but failed at the final stage. Nevertheless, we will continue to identify in the next year a high profile post-doc to be presented at INSERM.

Le Directeur du LAMC
Professeur Andreas BIKFALVI

Le Président de l'Université Bordeaux 1
Professeur Alain BOUDOU

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