Cellules souches normales et cancéreuses

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Normal and malignant stem cells

From the

University of Montpellier 1

INSERM

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Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

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Mai 2010

Research Unit

Name of the research unit: Normal and malignant stem cells

Requested label: UMR_S INSERM

N° in the case of renewal: U847

Name of the director: M. Bernard KLEIN

Members of the review committee

Chairperson

Mrs Annelise BENNACEUR-GRISCELLI, Université Paris 11

Other committee members

M. Claus Yding ANDERSEN, University of Copenhagen, Denmark

M. Francesco FRASSONI, Centro Cellule Staminali e Terapia Cellulare, Genova, Italy

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Report

1 • Introduction

- **Date and execution of the visit :**

The Institute for Biotherapy research (IRB) in Montpellier was visited on January 13, 2010. The visit was efficiently organized. After a general presentation by the director, the reports and projects of each of the teams were presented in front of all the unit members (lasted for each: 20 min, debate: 15/20 min). The organization of the visit provided time for separate discussions with the permanent staff members, the technicians and the post-docs and students out of the presence of the director or team leaders.

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

The Institute for Research in Biotherapy (IRB) is dedicated to the biology and clinical applications of normal and malignant stem cells in the area of translational research essentially.

The research unit is currently located in a new 16.5 M€ building (Inserm 1.5 M€; City 3 M€; CHU 6 M€ and Region 6 M€). From 2007 until today, the Unit included 2 teams: a team focusing on malignant plasma cell diseases and a team which focuses on embryo development and pluripotent stem cells. For the renewal of the Unit, two additional teams have been planned to join the unit: (i) a team of in the field of stem cell differentiation to hepatocyte and (ii) an emerging team from the CNRS IGMM Institute working on the anti-tumour immune response.

Fifty staff persons are working in the Inserm Unit (870 m2) which is evaluated. Together with the personnel working in the common facilities (658 m2), the University Hospital R&D structure (900 m2) and the private companies (470 m2) a total of about 120 personnel work at the IRB , 10 to 15 of them being also involved in clinical work. Further interactions between these groups are strengthened by the project presented for renewal of the unit.

- **Management team:**

The leadership of the director is considered excellent and efficient. It is believed that the present leadership will successfully be able to accommodate and integrate two additional research teams. The director aims to favour synergy between teams and the other structures of the IRB.

The leader already federates strongly the structure of the IRB with the development of common methodologies used by all the teams and has already organized common core facilities (L3, Transcriptome analysis, Proteomics, Bioinformatics). These core facilities appear to be well organized although some activities could probably be put more in common such as the preparation of vectors. Interaction with private companies and the support of the Hospital and the Regional Council are strengths that may help to support the development of the Institute in which the research unit is located. In addition, the two Universities in Montpellier identified regenerative medicine as a priority.

Strategy of investment are defined in agreement with the other institutes, university and university hospital.

Intellectual Property Rights are clearly an important priority of the IRB, ranked as the second priority after scientific innovation validated by publications. The Industrial Property is still a matter of debate between the Hospital and Inserm.

- **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)	6	11
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	5
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	12	12
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	8	12
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	3	3
N6: Number of Ph.D. students (Form 2.8 and 2.7 (future) of the application file)	7	7
N7: Number of staff members with a HDR or a similar grade	8	15

2 • Overall appreciation on the research unit

- **Overall opinion:**

The scientific projects of the Unit are original, pertinent and challenging. The heads of teams are well recognized in their field and each one is expected to successfully develop its projects. In general the projects of the Unit are mostly focused on translational research in agreement with the global strategy of the IRB which wants to develop patents and cell drugs or drugs that are clinically useful and economically competitive. However, while this strategy must be encouraged, basic science must be maintained for the long-term issues of the Unit. Globally, each team has ambitious projects and some priorities must be determined in accordance to the resources of the teams in order to be productive. It should be considered that some projects must be developed more transversally between the teams. For example team 3 should enhance its interactions with team 2 to use iPS in modelling hepatic disease and hepatic regeneration. Team 1 and 2 could share strategies and technologies to be more effective. Team 4 is a young emerging team that has to be reinforced by new recruitments and should synergize probably more with Team 1.

The development of iPSC is very new but it is moving toward a very competitive area. iPS is currently considered as a useful tool for the majority of the projects of the Unit. However, molecular markers of pluripotency that are explored by team 2 must be improved in the future by basic research and functional exploration studies.

- **Strengths and opportunities:**

The new building, close to the clinical and biological haematology units and other departments of the hospital, including facilities and private companies, represents an excellent opportunity and is well placed in that context. The gathering of 4 teams working on the same strategies using common techniques in the field of normal and malignant stem cells will certainly create fruitful synergy and promote creativity. The governance of the IRB and the strong involvement of the head of the Unit will be also decisive for a robust and long term development of the projects.

- **Weaknesses and threats:**

The main threat is that ES and iPS fields are very competitive fields in which it may be much more difficult to exist than in a translational research program focused on a specific disease, a program which has been very well conducted. Basic research on pluripotent stem cell should be reinforced to maintain a high level of competitiveness.

The number of young researchers in the unit is currently low, but several recruitments of researchers and teaching-researchers are planned. The planned recruitment is too often based on integration of people from Montpellier and should be more open to people from outside.

- **Recommendations to the head of the research unit:**

The aim to become a centre of GMP production of differentiated cells (i.e. hepatocytes or NK cells) for clinical trials is an important one but it is a time-consuming translational project, which is not realistic with the current organization. These projects must be transferred to a translational R&D laboratory with specific expertises in GMP culture.

The committee recommends the creation as a priority of one such structure with the help of the hospital and the University and a staff entirely dedicated to this activity in co-development with the private companies hosted in the IRB and the scientists of the Unit.

It appears important that the head of the Unit will have higher responsibilities as he is also the leader of the whole IRB. In four years from now, the age of the head of the unit will not allow him to start a new 4-year contract for the Unit. The next leader or the mode of recruitment of the next leader will have to be anticipated.

The Institute did not create its own advisory board so far to select projects to be developed and recruitment of new teams but such a creation is planned and highly recommended.

- **Data on the work produced :**

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

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	16
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	27
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	8
A5: Number of PhD granted during the past 4 years	7

3 • Specific comments on the research unit

- **Appreciation on the results:**

In the last 4 years, the unit has obtained results of a very good quality. Major accomplishments have been obtained in the knowledge of plasma cell diseases by the identification of genes associated with bad or good prognosis and in the role of some genes in cellular communication and proliferation. The description of the molecular characteristics of bone marrow stromal cells in Myeloma has been established and in vitro models to further characterize the molecular defect according to the hierarchy in the B lineage have been developed. In reproductive medicine, cumulus cells biomarkers have been identified reflecting oocyte and embryo developmental competence. In addition, a specific gene profiling of endometrium cells that could be deleterious to the embryo implantation has been defined. In the field of pluripotent stem cells, a technical research has been achieved with the derivation of French ESC and iPSC and transcriptomic analysis have now identified the role of the proteasome in the maintenance of pluripotency. The Unit on hepatocyte has isolated hepatocyte-like cells from the non-parenchymal compartment of the normal adult human liver. The two others major results concern the identification of cross talks between nuclear receptors and the role of tetraspanin CD81 in the hepatitis C virus entry.

There is a very good scientific production from the Unit: 188 publications for 32,7 full time equivalent researchers with 16 original publications IF > 10 and 5 patents.

Among the 188 publications 106 are from the Unit and the other arise from collaborations.

The teams have trained 20 PhD students and 8 post-doc researchers.

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

Researchers were recognized through 3 awards. Teams members have been invited to give 175 lectures for 2005-2009.

The new Inserm unit includes 2 new teams that were previously labelled by Inserm or Cnrs in a distinct setting. A candidate is identified to apply this year for an Avenir grant whereas a CNRS researcher may join the unit to deal with animal models. A young post-doctoral fellow, who joined team 1 two years ago, will apply for an Inserm position in 2010 and an Assistant Professor position will be proposed to another post-doctoral fellow in 2011. They have welcomed 9 visitors.

The 4 teams have obtained a 3,108,411 € funding for 2005-2009 and have already obtained 780,554 € for 2010.

The Unit is involved in EU or national grant reviewing (EU, ANR, INCA, Ligue, ARC, AFM) and obtained 3 EU FP6 or FP7 grants. Unit members are editorial board members of 3 journals and have organized 4 international meetings.

The Unit interacts mostly with French teams or European teams (MSCNET EU grant, Heidelberg) and some teams in US.

The international recognition of some of the teams may be improved.

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

The environment of the IRB and the proximity and collaboration with the hospital are very good assets. The head of the Unit plays a very active and dynamic role in the life of the research Unit and the IRB with the members of the CHU of Montpellier.

The Unit has obtained a large number of technicians and engineers (11,3 ETP tenure position). Some of them may be shared in common facilities in the coming years : 4,8 ETP are shared in common facilities.

The unit organizes twice a month meetings with outside or invited speakers that are open to Montpellier researchers or clinicians.

The members are responsible for various courses in the School of Medicine, of Pharmachemistry and University of Sciences, and managed 150 hours of Biotherapy courses.

Monthly strategy meetings are already organized between the teams, although they are still in different units.

- **Appreciation on the project:**

The strengths of the projects are the expertise of each team leader that gives a clear credit to the feasibility of some aspects of the projects. The projects are pertinent and tackle interesting questions. Globally the projects develop clinical tools for diagnosis, prognosis and treatment in cellular therapies and biotherapies. Some projects need to be improved by the development of functional in vitro or in vivo assays in order to enhance the knowledge of the molecular mechanisms.

The hESCs/hIPSCs is certainly a crucial aspect for the Unit to be supported as it will be very useful for a large number of projects of the Unit. The reinforcement of the human pluripotent stem cell part of the project, through

recruitment and the definition of more basic research questions, will minimize the risks for the development of a long-term scientific project.

The environment of the IRB with the core facilities and the technology of stem cells, the hosting of private companies and the easy access to human tissues and cell therapy unit are very good assets for the project of the Unit. The long-term collaboration with clinicians of the hospital has to be improved in order to rapidly transfer the results into clinical trials.

4 • Appreciation team by team

Team 1: Multiple myeloma cell plasticity, stem cells and niche

Team leader: M. Bernard Klein

- **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)	3	3
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)	8	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	2
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	2	2
N6: Number of Ph.D. students (Form 2.7 of the application file)	5	3
N7: Number of staff members with a HDR or a similar grade	5	5

- **Appreciation on the results:**

Team 1 is a well-recognized team in the field of multiple myeloma. In the last 5 years, this team has created a database in which gene expression profiles of newly diagnosed patients with myeloma (>200), cell lines, normal plasma cells and major components of the microenvironment have been included. This database was used for the identification of genes associated with a prognostic impact and novel tumour antigens. The team also explored the function of Syndecan-1 and various cytokines (BAFF/APRIL, IGF-1, IL-6) in disease progression and developed an in vitro 3-step model of multiple myeloma to explore their function. They also demonstrated that bone marrow stroma cells in patients with MM could play an important role in driving the evolution from MGUS to MM and a specific expression of cytokines has been identified. Lastly, the team has set up a phase I/II clinical trial targeting BAFF with TACI-Fc (limited toxicity and some efficacy) and another trial with anti-IL6 antibodies.

The team itself has produced 60 publications in the last 5 years, 30 of which involving a member of the team as a first and/or senior author. 22 publications had an IF > 3, 12 with a FI > 6 and 6 with a FI > 10 (J Clin Oncol x 1, Blood x 5). These publications were mainly in specialized journals (Blood, Oncogene, Clinical Cancer Res, Haematologica, Br J Cancer x 1, Br J Haematol, BMC bioinformatics, BMT, Exp Hematol.) and sometimes in Immunology Journal (JI x 4). The team is associated to 30 papers, including 22 with a FI > 3, and 6 with a FI > 10 (Nature Immunol, Blood x 5).

The major and original contributions of the team during the last 4 years in the biology of myeloma gave rise to 7 publications in excellent journals with high impact factors (Blood (10,4), Imunol.rev (10,5) and JCO (IF15,5).

The team leader has given 23 invited conferences. Finally, the team has produced two patents.

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

This work has been conducted by a small group (5 researchers - 2,5 ETP – 3 with teaching duties) and since 2007, the team has recruited 1 assistant professor, 2 technicians through the University and 2 time-limited contracts. On the other hand, the team includes one Inserm permanent researcher (CR1) and 4 post-doctoral fellows. The team has also an excellent network of interactions, especially close with Germany (very strong interaction with Pr Goldschmidt in Heidelberg, 27 joint publications) but also in France (Pr Bataille), US (B. Barlogie and J. Shaughnessy) and other European centres (MSCNET EU grant). The institute hosts several private companies, which synergise with the team.

- **Appreciation on the strategy, governance and life of the team:**

The team collects a large amount of money through grants from a number of organisms (Funding 2007-2009 = 1.151k€, 2010 – 252 k€).

Five students have defended their PhD and five others are working in the team, which includes 5 HDR.

The team leader and researchers are involved in teaching and in the organization of courses in cell therapy.

- **Appreciation on the project:**

The project presented remains dedicated to multiple myeloma, which is still a fatal disease. The written project included eight distinct aims, many of them being in the line of the previous work including biological follow-up of patients and upgrading of the database to 500 patients, identification of genes with a prognostic impact, functional analysis of these genes, characterisation of circulating multiple myeloma cells, role of osteoclasts in multiple myeloma cell niche, in vitro plasma cell generation, multiple myeloma cell plasticity and clinical trials. This program has been presented orally in two parts. The first one is dedicated to the identification of the myeloma stem cell and stem cell niche (which includes normal plasma cell differentiation, the characterization of circulating multiple myeloma cells, the analysis of plasma cell plasticity, characterization of the myeloma niche (including stromal cells and their role in driving the disease) and the development of an animal model); the second is dedicated to gene products that are critical for MM biology with clinical applications.

- **Conclusion:**

Overall, team 1, which is the leader team of the unit, has very original results and a large program whose specificity in the field is to be based on gene expression rather than genetic mutations or alterations. Another interesting aspect is the identification of the myeloma stem cells and their environment. These are already strong lines of research, which are likely to bring about new interesting developments. Banking of multiple myeloma samples used for microarray studies may be useful to follow technology upgrades (miRNA arrays, exon arrays, deep sequencing).

Weaknesses include the high number of genes whose alteration and prognostic value has been identified and whose function has still to be deciphered in the plasma cell context, the difficulties to develop animal models and preclinical studies to test combinations of innovative approaches (TACI-Fc, Anti-IL6) with currently used drugs (bortezomib, dexamethasone and others), and the limited expertise in analyzing signalling pathways. The team has also developed an in vitro model for studying the transition from B cells to Plasma Cells (PC). This may have a relevant impact in understanding Myeloma development at the cell level.

- **Recommendations:**

The leader of the team is strongly encouraged to prospect rapidly for a new team leader in the next four years to preserve the continuity of this topic in the unit.

Team 2 : Early embryo development and human embryo stem cells

Team leader: M. S. Hamamah

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	3	4
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	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	2
N7: Number of staff members with a HDR or a similar grade	3	4

- **Appreciation on the results:**

The team has been created in 2008 (first evaluation in 2007) and has two main research projects. The first is related to assisted reproduction and focuses on the identification of biomarkers that could predict receptivity to eggs, looking for the predictive value of cumulus and endometrium transcriptome. The second topic concerns early human development and aims at understanding the extracellular signalling pathways that contributes to the maintenance of pluripotency, to create and maintain pluripotent cells in vitro.

The major contribution of the team in the last 4 years has been the identification of candidate genes and proteins in oocyte in relation with human oocyte maturation and hyperstimulation protocols. The team has derived 4 new hESC lines from normal and PGD embryos and established a pluripotency signature. It has also created a web expression Atlas focusing on pluripotency (http://amazonia.montp.inserm.fr).and identified new membrane bound pluripotency markers such as CD24 or SEMA6. (article in Human reprod IF 3,77, stem cells IF 7,5).

Overall, the results presented by Team 2 are of good quality and they are internationally competitive in the context of reproductive medicine. While the projects developed by the research projects are not very innovative, they should bring about useful and important results for the improvement of In Vitro Fertilisation (IVF) procedures. However, there are several aspects that would need to be improved.

The projects are rather descriptive and should include more functional studies, focusing for example on some of the genes identified as biomarkers of endometrial receptivity.

It is important that Team 2 reinforces significantly the project concerning pluripotent stem cells, otherwise this part of the team will not be competitive. In addition, there should be a biological question underlying the iPS part.

Team 2 would also benefit from international collaborations, which could help Prof. Hamamah to validate the approach and the questions asked by his group.

Team 2 have generated 50 publications in journals well established in this field, half of them (24) stem directly from their own research. The team has trained 3 PhD, one HDR.

The head of the team is regularly invited to give seminars. Most of these seminars target clinicians working in the IVF field. Team 2 should try to participate more frequently to international meetings in order to develop a broader network of collaborations.

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

The head of Team 2 has received several prizes. The members of the group are clearly involved in different activities outside the unit (teaching, organisation of the GMP facility, etc…). The team has not enough full time researchers, which is an issue especially for the long-term development of further projects focusing on stem cells. Indeed, the stem cells field is extremely competitive and any projects on this subject will require additional resources to be successful. Thus, the recruitment of a post doc would be beneficial, especially if this person is recruited outside France. Indeed, there doesn't appear to be any foreign scientists and/or post-docs and/or Ph-D students in this team.

Team 2 has also submitted one patent demonstrating their interest to interact with industrial partners. In addition, Team 2 is planning several clinical trials, which should provide further opportunities to develop collaborations outside the Montpellier area.

- **Appreciation on the strategy, governance and life of the team:**

Team 2 is driving two separate research projects and this aspect could be problematic. Indeed, the main project focuses on developing methods to improve IVF efficacy while the second part focuses on human pluripotent stem cells (human Embryonic Stem Cells and human induced Pluripotent Stem cells). There are no direct scientific links between the two projects and this situation has clearly limited the development of ambitious projects on stem cells. Further efforts are required to balance this situation.

- **Appreciation on the project:**

Team 2 is planning to develop interesting projects and important results will be generated in a near future, and there is no doubt that some projects will be successful in the long term. One important issue remains the scientific relationship between projects focusing on IVF and the projects focusing on hESCs/hIPSCs.

Team 2 has also to reinforce its full time research activity on both of its main topics. One aspect would be to develop a functional validation of the genes they have identified as predictive biomarkers for embryonic development after in vitro fertilization or to include other more innovative approaches (spliceosome, miRNA…). Concerning the second research project on ES cells and iPS, efforts should be made to identify a long-term project with specific aims that could be more ambitious than the development of new cell lines and the identification of genes differentially expressed during reprogramming. It is very important to conserve and strengthen this specific expertise in the Montpellier area. Such expertise on ES and iPS cells will moreover bring essential knowledge to other teams and is essential for the unit as a whole.

- **Conclusion:**

Team 2 is a well organised research group with a good productivity. Team 2 is associated with an IVF unit, a situation which is relatively rare and should accelerate the development of clinical applications in the field of regenerative medicine. Therefore, the expertise and the projects developed by Team 2 have to be supported.

However, the development of two separate themes could be an issue. The stem cells part will need more support especially since it represents a key aspect for the rest of the unit. Indeed, hESCs/hIPSCs could be very useful for a broad number of projects developed by Team 1-and 4.

The recommendations are:

- To reinforce the international visibility of the Team through collaborations, meetings and networks participation, and recruitment (see below).

- To recruit full-time researchers.

- To develop collaboration with other teams and to develop synergistic approaches that will enhance the global output of the team.

- To reinforce the human pluripotent stem cell part, through recruitment and by defining more specific aims and scientific questions.

- To enhance the leadership by enhancing the participation to international conferences.

Team 3 : Hepatic Differentiation of Stem Cells and Biotherapy of Liver Diseases

Team leader: Martine Daujat

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	2
N7: Number of staff members with a HDR or a similar grade	6

- **Appreciation on the results:**

Team 3 has a long and strong expertise in the field of human hepatocyte primary culture, xenobiotic metabolism and detoxication. In the last past years, the major contribution in the field was the isolation of hepatocyte-like cells from the non-parenchymal compartment of the normal adult human liver. The other two major results concern the identification of cross talks between nuclear receptors and the role of tetraspanin CD81 in the hepatitis C virus entry. (articles in J hepatol, IF 7,06; Stem cells 7,74; Hepatology IF 11,35, Gastroenterology IF 12,59). These two latter axes will not be pursued in the future team.

The team has been involved in 72 publications in the last 5 years, among which 47 come from the team research subjects with an average IF of 5.55 and 5 publications in the Top 1%, 7 in Top 10% and 3 in Top 20%. The publications are mainly in high ranked specialized journals (Gastroenterology, Hepatology, J. Hepatol, Drug Metab Rev., J. Virol) and sometimes in high ranked general journals (J. Clin Invest, Plos One). There is no patent.

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

The team has an international recognized expertise in molecular pharmacology and human hepatocyte primary culture. Team members have numerous invited conferences but invitations to international conferences involve only one member of the team who is not the team leader.

The team is comprised of 3 PUPH, 1 MCUPH, 1PH, 2 CR1 and 1DR1 (who used to be the director of the previous team and who will retire in the next four years), 2 engineers and 2 technician. Since 2007, the team has recruited an INSERM engineer. A young post-doctoral fellow will apply for an EPST position.

Four students have defended their PhD and 4 are still actually working in the team (6 HDR).

The team is currently correctly funded (500 k€) with a European Grant and a collaborative INCA grant. However, it should be underlined that the main future project of the team is not yet funded.

- **Appreciation on the strategy, governance and life of the team:**

The presented project is dedicated to the differentiation of stem cells (iPS, ES and Hepatic Progenitors) towards hepatocytes and the study of homing and survival of transplanted hepatocytes in a biotherapy prospect. It is not a particularly original project but it is an interesting one. The environment of the IRB with the expertise of team 2 on ES and iPS and the proximity and collaboration with the hospital are very good assets. The expertise of team 3 on hepatocyte differentiation gives a clear credit to the feasibility of some aspects of the project.

- **Appreciation on the project:**

This is a huge project that has to be prioritized: each axis is a whole research program in itself, for example the epithelial-mesenchymal transition or the involvement of hepatic progenitor cells in the development of hepatocellular carcinoma. In the same line, the generation of iPS from human hepatic cells addresses a more general question (Are reprogrammed cells derived from a specific cell type more permissive to this cell type differentiation?) that is probably beyond the scope of this project and represents a program in itself. The specificity of the group, which has isolated non-parenchymal hepatocyte progenitor cells and has all the background to study the maturation of stem cells, has to be pushed forward.

Finally, the aim to become a centre of GMP hepatocyte preparation is an important but time-consuming translational project that would require a staff entirely dedicated to it.

- **Conclusion:**

The overall appreciation of team 3 is good with an interesting project that is however too large and has to be prioritized.

The strengths are the expertise of the team on human hepatocyte differentiation which is quasi-unique in France and the feasibility due to the environment, on the one hand inside the IRB with ES and iPS technology and technological platforms, and on the other hand inside the hospital with a long-term collaboration with clinicians.

The weaknesses are the current level of publications of the team in the stem cell field, the leadership that has to be improved to maintain competitiveness and too large a project.

The committee recommends:

- To precisely define priorities in their project by focusing on some aspects in which the team is a recognized expert i.e in hepatocyte differentiation. It would be otherwise detrimental for keeping a position in this very competitive field.

- To develop collaborations in the stem cell field at the European level.

- To apply for funding in the stem cell area.

- To participate at a higher level to international meetings and publish in higher ranking journals particularly for the team leader who has to establish her leadership.

Team 4 : Immune system control of hematological neoplasias

Team leader: M. Martin Villalba

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

- **Appreciation on the results:**

Team 4 is a small team headed by a CNRS Researcher who initially analyzed a model of PKC theta deficient mice with defective immune response and obtained still unexplained results when leukemic cells with PKC theta deficit were injected into immuno-competent animals in which they failed to develop. The major contribution of the researcher has been the understanding of the role of ERK5, which may be specifically expressed or overexpressed in some lymphoid leukemic cells. ERK5 is involved in IL-2 expression and accumulates in the nucleus to transactivate NFkB p65. ERK5 was shown to inhibit death-receptor induced apoptosis and shRNA targeting ERK5 could favour induction of an immune response. Recently, the group also explored JunB mediated transactivation and the role of SUMOylation in this effect (3 J. Immunol IF 6).

The proposed project includes 3 parts. 1) ERK5 and the bioenergetic profile of normal and leukemic cells; 2) ERK5 and MHC-class I regulation; 3) NK cells for clinical use in treating acute leukemias.

The two first points of the program may clarify some contradictory results as the group showed that ERK5 down-regulation favoured cell death, which could also trigger an immune response. ERK5 down-regulation also induces a decrease in MHC class I expression, which may prevent an adapted immune response. The link is made with metabolic changes in the cells and the synthesis of MHC class I. The team will have to clearly define the relevance of ERK5/MHC class I pathway in human leukemias and to determine which subgroup is concerned.

The third part of the program deals with the amplification and activation of NK cells with a therapeutic grade using attenuated or genetically modified tumour cells.

In the last years, the program generated 5 publications from the team itself (J Immunol 2009, 2008, 2006; Mol Immunol 2008; Scand J Immunol 2005) and another one in a collaboration (J Immunol 2009), which is a correct record for such a small group. Additional results are currently in revision. The team also claims 1 patent, 6 invited conference and 3 PhDs supervision.

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

This work is conducted by the team leader with 1 CNRS engineer, two clinicians, 1 PhD student and 2 Master students.

The team is applying for money in order to recruit 3 post-doctoral students. A post-doctoral fellow will apply in 2010 for a tenure position (CNRS) and another one is still in formation in the US and is planned to be recruited.

In 2007-2009 the team has collected a good amount of money through grants from a number of organisms (~300 k€) and has already secured over 80k€ for 2010.

- **Appreciation on the strategy, governance and life of the team:**

This is a new and small team, which is in the process of joining the research unit. In the next year, the team leader wants to hire with the help of the director 2 staff members for tenure position (2 candidates have been already contacted).

The project is relevant taking into account that this team will have strong interactions with the Hematology Unit (2 clinicians are involved in this team).

No teaching activities described but 2 master students are already in this team.

- **Appreciation on the project:**

The investigation on the pathway ERK → MHC class I is interesting but still very preliminary. However, the characterization of the mechanisms by which ERK5 downregulations induced metabolic changes in tumour cells as well as the study of the molecular basis of respiration-induced MHC class I upregulation should be strongly reinforced before envisioning the development of NK-based immunotherapy in the treatment of leukemia relapse.

Nevertheless, the scientific expertise of the team makes this project feasible and original.

- **Conclusion:**

This is an interesting project with potential clinical application that can be envisioned thanks to the tight link between the research unit and the Haematology Unit. However, data concerning the NK project appear too preliminary before going into clinical applications.

The strengths of this team include the identification of the specific kinase (ERK5) over-expressed in some leukemia cells and the link with MHC class I molecules which may offer the possibility to develop NK-based immunotherapy in leukemia relapse following cord blood transplant (CBT). Other strengths are the connexion with other teams in the unit, the clinical haematology department and the cellular therapy lab in the hospital to develop NK cell production.

The main weaknesses are the poor knowledge of the pattern of ERK5 over-expression in acute or chronic leukemias in humans and the poor general scientific background, which makes the working hypotheses very fragile.

In addition there is not enough research of post CBT immune reconstitution.

There is not enough research on NK either and more scientific background on NK is needed.

The team has not an evident skill in manipulation of NK in the clinical setting.

- **Recommendations:**

- To consolidate the proof of concept concerning the effect of ERK on MHC class I expression in various leukemic models in mice and human.

- To reinforce the study of oxygen metabolism in leukemia before going into clinical applications that come probably too early in the program.

- To increase the number of people involved in this task.

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**

Nom de l'équipe : *MULTIPLE MYELOMA CELL PLASTICITY, STEM CELLS AND NICHE*

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

Nom de l'équipe : *EARLY EMBRYO DEVELOPMENT AND HUMAN EMBRYO STEM CELLS*

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

Nom de l'équipe : *HEPATIC DIFFERENTIATION OF STEM CELLS AND BIOTHERAPY OF LIVER DISEASES*

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

Nom de l'équipe : *IMMUNE SYSTEM CONTROL OF HEMATOLOGICAL NEOPLASIAS*

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

Administration Droit Economie Gestion Médecine Odontologie Pharmacie Sports

UM1
Université Montpellier 1

Montpellier, le 15 avril 2010

Le Président
Ph.A/NG
Départ 2010 - 217

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Agence d'Evaluation de la Recherche et de
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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 de recherche **«Biothérapie des cellules souches normales et cancéreuses»**

Vous trouverez ci-joint les réponses du Directeur de l'unité auxquelles le Vice Président du Conseil Scientifique et moi-même n'avons aucune remarque particulière à rajouter.

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

Philippe AUGE

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INSERM-UM1 Unité 847
BIOTHERAPIE DES CELLULES SOUCHES NORMALES ET CANCEREUSES
BIOTHERAPY OF NORMAL AND MALIGNANT STEM CELLS
Directeur : Professeur Bernard Klein

Reply to AERES comments

General comments. All team leaders and researchers fully agree with the comments of the committee who performed a detailed evaluation of our project and organization, of our strength and weakness. The committee recommendations will help us to prioritize some fields.

1. Overall appreciation on the research unit

Weaknesses and threats

"*The main threat is that ES and iPS fields are very competitive fields in which it may be much more difficult to exist than in a translational research program focused on a specific disease, a program which has been very well conducted. Basic research on pluripotent stem cell should be reinforced to maintain a high level of competitiveness.* "

We fully agree with the committee that our current major strength is to use well defined ES or iPS cell lines to further improve our unique expertise in some physiopathological fields, *i.e.* oocyte and its niche and hepatocyte physiology. Thus, given the importance of getting our own ES or iPS cell lines, in particular for patenting issues, the priority 1 of the unit will be to go on obtaining GMP-derived ES or iPS cell lines in connection with EU laboratories in this field. One full time technician is devoted to this field.

The contribution to the understanding of the basic mechanisms involved in pluripotency will be developed by Team 2 only if we can get enough funding and recruit full time researchers to be enough competitive.

"The number of young researchers in the unit is currently low, but several recruitments of researchers and teaching-researchers are planned. The planned recruitment is too often based on integration of people from Montpellier and should be more open to people from outside."

The committee is right and our priority is to attract outside scientists who have acquired experience in international institutes. The Unit is located in a new institute whose research is acknowledged and with well-equipped platforms and we are now receiving more and more applications of outstanding scientists to enter the unit.

Recommendations to the head of the research unit

"The aim to become a centre of GMP production of differentiated cells (i.e. hepatocytes or NK cells) for clinical trials is an important one but it is a time-consuming translational project, which is not realistic with the current organization. These projects must be transferred to a translational R&D laboratory with specific expertise in GMP culture. The committee recommends the creation as a priority of one such structure with the help of the hospital and the University and a staff entirely dedicated to this activity in co-development with the private companies hosted in the IRB and the scientists of the Unit."

The committee is fully right. This was not well explained in the project but this translational R&D laboratory does already exist in the Cell Therapy Unit of the University hospital that is located 50 meters from the IRB. This cell therapy unit has been created by the head of the Unit, is now supervised by Dr De Vos, an active unit member, and has 380 m2 clean rooms, some of them dedicated to pre-clinical development.

"It appears important that the head of the Unit will have higher responsibilities as he is also the leader of the whole IRB. In four years from now, the age of the head of the unit will not allow him to start a new 4-year contract for the Unit. The next leader or the mode of recruitment of the next leader will have to be anticipated."

The committee is right. The head of the research Unit should also be the head of the IRB for a question of management efficacy. The head of IRB has been appointed in 2007 after an international call published in September 2006 and evaluation by an international scientific committee. This is a written rule of the inner regulations of IRB defined by the 3 partner institutions: INSERM, University Montpellier I and University Hospital. There will be an international call in October 2012 and appointment in May 2013, 6 months before the submission of a new 4-years project in October 2013.

"The Institute did not create its own advisory board so far to select projects to be developed and recruitment of new teams but such a creation is planned and highly recommended."

The advisory board has been created and has selected IRB director and then the teams which are now located at IRB, in September 2007. The committee will meet in 2012 again to evaluate the current projects of the INSERM-University units as well as the hospital laboratories.

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

"The environment of the IRB and the proximity and collaboration with the hospital are very good assets. The head of the Unit plays a very active and dynamic role in the life of the research Unit and the IRB with the members of the CHU of Montpellier. The Unit has obtained a large number of technicians and engineers (12,5 ETP), most of them (~10) with a stable position. Some of them may be shared in common facilities in the coming years."

We have to emphasize that 7 technicians and engineers with stable position are already working on common facilities.

Appreciation team by team

Team 1: Multiple myeloma cell plasticity, stem cells and niche
Team leader: M. Bernard Klein

The committee recommends:

« Weaknesses include the high number of genes whose alteration and prognostic value has been identified and whose function has still to be deciphered in the plasma cell context, the difficulties to develop animal models and preclinical studies to test combinations of innovative approaches (TACI-Fc, Anti-IL6) with currently used drugs (bortezomib, dexamethasone and others), and the limited expertise in analyzing signalling pathways. »

1. The reviewer is right that there are high number of genes whose alteration and prognostic value has been identified (about 200 genes). But this is the case for all competitors in this field and our creativity will be to select the most promising ones to demonstrate their relevance in plasma cell biology.

2. There is no reproducible animal model of human multiple myeloma as indicated in the project and during team 1 oral presentation. Team 1 is now recruiting one tenure researcher who is an expert in animal models (waiting for INSERM agreement) and will extend its original animal model using our own agonist anti-gp130 monoclonal antibodies (Blood, 1999) in Nod SCID IL-2R$\gamma^{-/-}$ mice. This was indicated in the written project and mentioned in the oral presentation.

3. This point was likely not clearly emphasized in the written project. But Team 1 has a correct expertise for cell signaling using current protein analysis (western, Immunoprecipitation, FACS) and now the large amount of commercially-available methods and compounds that make these studies easier and easier. As examples, all the techniques for studying the pro- and anti-apoptotic proteins, the cell cycle proteins, the major signaling pathways involved in myeloma have been mutualized and standardized in team 1 with written approved protocols. They are routine techniques in the laboratory. In addition, we fully master the building of lentiviruses making it possible to transduce gene with inducible promoters .

Recommendations. *« The leader of the team is strongly encouraged to prospect rapidly for a new team leader in the next four years to preserve the continuity of this topic in the unit. »*
This is the priority of the team leader. Two tenure researchers (40 years old) want to join the team and two postdocs are applying for tenure positions.

Team 2 : Early embryo development and human embryo stem cells. Team leader: M. S. Hamamah

The committee recommends:

1. *To reinforce the international visibility of the Team through collaborations, meetings and networks participation, and recruitment (see below).*
2. *To recruit full-time researchers.*
3. *To develop collaboration with other teams and to develop synergistic approaches that will enhance the global output of the team.*
4. *To reinforce the human pluripotent stem cell part, through recruitment and by defining more specific aims and scientific questions.*
5. *To enhance the leadership by enhancing the participation to international conferences. »*

Points 1. and 3. and 5. We collaborate actively with International experts (i.e. Pr HOVATTA from the Karolinska Institute, 2 papers already published together: Stem cell 2007, BMC genomic 2009; Dr Mamoud from Tunisia: 4 papers in Human reproduction, 2008; and 3 in 2009). The head of the team is regularly invited to give lectures during national and international congresses and not seminars. Team 2 participates frequently to international, major meetings in its field such as ESHRE, ASRM, ISSC (67 oral communications and posters between 2005 and 2009). Team 2 organizes on May 5-8th 2010 the 10th preimplantation genetic diagnosis congress. More than 400 peoples are expected.
Points 2. and 3. Dr John De Vos (in charge of the pluripotency project) is actively requesting for grant support and recruiting outstanding scientists to assist him in developing this competitive pluripotency project. One Canadian post-doc will join his group soon.
Given the unique expertise and originality in oocyte-cumulus interaction of Pr Hamamah who is the head of the In vitro Fertilization department of the University Hospital, it is a priority of the Unit head to recruit a tenure researcher to strengthen this project. As an example, team 2 has identified and patented gene signature of cumulus cells that could

predict for the fertilization potential of the corresponding oocyte. The cumulus cell lines are being immortalized providing a unique material to further study the role of the most promising gene products.

Team 3 : Hepatic Differentiation of Stem Cells and Biotherapy of Liver Diseases
Team leader: Martine Daujat

The committee recommends:

1. To precisely define priorities in their project by focusing on some aspects in which the team is a recognized expert i.e in hepatocyte differentiation. It would be otherwise detrimental for keeping a position in this very competitive field.
2. To develop collaborations in the stem cell field at the European level.
3. To apply for funding in the stem cell area.
4. To participate at a higher level to international meetings and publish in higher ranking journals particularly for the team leader who has to establish her leadership.

Points 1 and 2. We agree with the committee that our overall project is too large and has to be prioritized.
Three projects have been presented:
Project 1 on the differentiation of stem cells/progenitors into functional hepatocytes,
Project 2 on the relationship between liver progenitors and hepatocellular carcinoma
Project 3 on the GMP production of hepatocytes and liver biotherapy.

- Our priority N°1 will be project 1, focusing on the improvement of the terminal differentiation of human liver progenitors/stem cells into mature hepatocytes and on the molecular pathways involved in the differentiation process. More than 50% of full time equivalent researchers will be dedicated to these aspects. A close collaboration based on the codirection of a phD student has been developed in this respect with Cecile Legallais (UTC Compiegne), expert in tissue engineering and 3D cultures.
The generation of IPs from human hepatic cells does not represent a priority and will be developed synergistically with team 2.

- Our priority N°2 will be project 3. Technical modifications of our protocol for the GMP preparation of human hepatocytes are under progress. At the end of 2010, as soon as the quality of human hepatocytes recovered by this process will be established, the technology will be transferred to the Unit of Cellular Therapy (St Eloi Hospital) which will become the centre of GMP production of hepatocytes.

- Our priority N°3 will be project 2, which comprises ongoing collaborative themes in which our team is already involved and funded. 25% of full time equivalent researchers will be involved. The investigations on progenitor differentiation are at the center of both the French Inca and European MARCAR collaborative projects. Our contribution in these projects focuses on the study of the impact of etiological agents of hepatocellular carcinoma on hepatocyte and liver progenitor differentiation. The EMT project is not a priority and will be developed through a collaboration with Nathalie Bonnefoy-Berard.

Point 3. This is under current programming, targeting not only public research agencies/institutions but drug industries as well.

Point 4. It's right that team leader has to promote the team's work through participation to international meetings and through production of high quality publications.
Team leader has been invited as a speaker to present Stem Cells as Tools for Studying Xenobiotic Metabolism at: the 18th International congress of Microsomes and Drug Oxidations (Beijing, China may 2010), the 9th International Meeting of ISSX (Istanbul, Turkey september 2010) and the 2nd Hepatocyte User Group Meeting (Montpellier october 2010). A manuscript on the differentiation of human embryonic stem cells into hepatocytes is under current submission to Stem Cells.

Team 4 : Immune system control of hematological neoplasias.
Team leader: M. Martin Villalba

The committee recommends:

"1. The main weaknesses are the poor knowledge of the pattern of ERK5 over-expression in acute or chronic leukemia in humans and the poor general scientific background, which makes the working hypotheses very fragile.
2. In addition there is not enough research of post CBT immune reconstitution.
3. There is not enough research on NK either and more scientific background on NK is needed.
4. The team has not an evident skill in manipulation of NK in the clinical setting."

Point 1. The pattern of ERK5 expression in hematopoietic tumor cells has not been investigated in detail. However, ERK5 is expressed in all tested hematopoietic tumor cell lines from human or mouse origin [1-3] and in primary tumor cells of hematopoietic origin i.e. multiple myeloma [4] or Bcr-Abl expressing cells [5]. ERK5 expression is essential for survival and proliferation of these tumor cells [1-5], but not naïve T cells of mouse origin [6]. Moreover, we have shown that miR-143 targets ERK5 [7]and the expression of this miR is decreased in most of the B-cell malignancies examined, including chronic lymphocytic leukemia (CLL), B-cell lymphomas, Epstein-Barr virus (EBV)-transformed B-cell lines, and Burkitt lymphoma cell lines [8]. Moreover, the introduction of either precursor or mature miR-143 into Raji cells resulted in a significant growth inhibition that occurred in a dose-dependent manner and the target gene of miRNA-143 was determined to be ERK5 [8].

References:

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3. Charni, S. et al. ERK5 knockdown generates mouse leukemia cells with low MHC class I levels that activate NK cells and block tumorigenesis. J Immunol 182, 3398-405 (2009).
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Our results on the control of cell metabolism by the ERK5 pathway could explain this essential role of ERK5 in these cell types. We would like to stress that this part of our project is not dedicated to investigate the expression levels of ERK5 in leukemia cells but to investigate the physiological role of the protein, why it is essential and how it directs leukemogenesis. Our published and unpublished results show that:

i) ERK5 controls tumor cell metabolism
ii) ERK5 controls MHC-I expression and therefore plays an important role in immune system tumor evasion

These two phenomena are linked and our results could explain why changes in metabolism and missexpression of MHC-I are two markers of tumorigenesis.

Point 2. Team 4 is going to collaborate with team 1, the Service of Hematology and Biotherapy and the Cell Therapy Unit to develop this point.

Point 3. The group leader is establishing collaborations with experts in the NK cell field. He is already the coordinator of a program financed by the "Communauté de Travail des Pyrénées". This program includes Dr. Alberto Anel from the University of Zaragoza that is an expert in CTL and NK cell killing. The group leader is presenting a project as co-ordinator to the SUDOE program of the EU. The consortium includes several experts on NK cell field: Drs. M. Lopez-Botet, C. Vilches, A. Anel and A. M. Caminade. Therefore, the group leader is actively working on eliminating this problem. But, we would like to stress that the group leader has already published two papers in the NK cell field.

Point 4. The committee is right and it is clearly a point we have to reinforce. This will be done in close collaboration with the biologists of the Cell Therapy Unit and team 1. Indeed, Team 1 head and his biologists, when in charge of the Cell Therapy Unit, have already developed Afssaps-agreed clinical trials with ex vivo amplified Tumor Infiltrated Lymphocytes and have started to develop NK cell amplification clinical grade strategies. If team 4 is created by INSERM, this project will be started again by the Cell Therapy Unit, in collaboration wit the new head (Dr De Vos) and team 1 leader.

Recommendations

1. To consolidate the proof of concept concerning the effect of ERK on MHC class I expression in various leukemic models in mice and human

Regarding humans, we will develop this project in collaboration with the Service of Hematology and Biotherapy. Team 1 is recruiting an expert in animal models and we hope to develop the proof of concept in murine models in collaboration with the selected researcher.

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2. *To reinforce the study of oxygen metabolism in leukemia before going into clinical applications that come probably too early in the program*

We will develop a deeper basic study in this topic before developing clinical applications. However, together with the Service of Hematology and Biotherapy we will start investigating the possible correlation between diet and MHC-I expression in human patients. This will be a simply descriptive and small project.

3. *To increase the number of people involved in this task.*

There are two postdoctoral fellows in training in the USA that are presenting to CNRS and INSERM commissions to join our group. The group leader has obtained fundings to cover a post-doc position for 18 months.

Montpellier, April 12th, 2010

Bernard KLEIN
Directeur du laboratoire INSERM-UM1 U847