Hématopoïese et cellules souches

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research Unit :

Normal and pathological hematopoiesis

University Paris 11

March 2009

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Le Président de l'AERES	Section des unités de recherche
	Le Directeur
Jean-François Dhainaut	**Pierre Glorieux**

March 2009

Evaluation report

Research Unit :

Name of the unit : Normal et pathological hematopoiesis

Requested Label: INSERM UMR_S

N° in case of renewal : U790

Name of the Director : M. Eric SOLARY (former director : M. W. Vainchenker)

University or School:

University Paris 11

Other institutions and research organization:

Institut Gustave Roussy

Date of the visit :

November 20th 2008

Members of the visiting committee

Chairman of the commitee :

M. Daniel OLIVE, University of Méditerranée-Aix Marseille 2

Other committee members :

Mme Susan CHAN, University of Strasbourg 1

M. Franck Emmanuel NICOLONI, University of Lyon

M. Gérard SOCIE, University of Paris 7

M. Doug HIGGS, University of Oxford

M. François-Xavier MAHON, University of Bordeaux 2

CNU, CoCNRS, CSS INSERM, représentant INRA, INRIA, IRD.....) representatives :

M. Bernard PAYRASTRE, représentant des CSS de l'INSERM

Aucun représentant du CNU suite au désistement de l'expert initialement prévu

Observers

AERES representative

M. Frédéric FLAMANT

University or school representative:

M. Dominique EMILIE, Université Paris 11

M. Gilbert LENOIR, Institut Gustave Roussy

Research organization representative (s) :

Ms Christine TUFFEREAU, Chargée de mission de l'INSERM

1 • Short presentation of the research unit

The unit include 40 members including :

-10 researchers with teaching duties : 2 PUPH, 4 MCUPH, 4AHU

-9 researchers ;

-4 M.D. (2.5 FTE);

-9 technicians including 4 CDD (8. 8 TFE);

-12 Ph.D students

11 unit members have a HDR and 2 have a PEDR

18 students obtained their PhD during the 4 past years, including 7 MD and PharmD

Among the 19 researchers with a permanent position 18 are publishing.

2 • Preparation and execution of the visit

The visit was held at IGR pavillon de Recherche. The project was presented by the head of the unit. Then the three team leaders presented their projects. The committee members then met the PhD , post docs, researchers, technicians. The committee discussed with the representatives of University of Paris 11 and of the Medical Faculty as well as the scientic director of the IGR. Then, the committee members had a final meeting with both the previous and future directors. The presentations were well organized with the opportunuty to listen to team leaders as well as junior scientists. The committee had thorough and extensive discussions on most aspects of the projects as well as on the management of the research and its integration within the IGR research campus. Lab leaders who were about to join IGR and collaborating with them were also present during the presentations.

3 • Overall appreciation of the activity of the research unit, of its links with local, national and international partners

This unit was founded in 1992 and was highly successful during the last 16 years. The major evolution for 2010 corresponds to :

One scientist will leave, one will now be associated to Team 2. 3 teams are proposed.

The new director is Pr. In Dijon but his Hospital duties depends now on IGR. He heads in Dijon the « Centre de Recherche Lipids, Nutrition and Cancer »INSERM UMR866. He is already in charge of the project named Integrated Research Cancer Center that will replace IFR54. Among the goals of the IRCC will be to integrate all forms of cancer research (clinical, translational, epidemiologic, technical and fundamental). Among the priorities they organize the facilities with the University Paris 11 and IGR including imaging and animal facilites that are critical for the project proposed by U790. The new director is perfectly suited for the project based upon his previous achievements in Dijon, his recent efforts in the IRCC project, his excellent integration in the field of translational research in Hematology. Altogether, he should permit to reach an even better development of the lab together with IGR and the University Paris 11. One of the critical issues that is being discussed is the creation of a professor position at the University Paris 11 for the director. This is currently proposed and discussed. A tentative schedule could be to have the Professor position in 2011. However, this issue still has to be solved.

The lab is among the international leaders in the field of Hematology research. It gathers most of the major researchers in the field of stem cell research as well as identification of the genetic basis of hematological disorders. The future lab should even increase its efficiency thanks to the planned arrival of “génétique des hémopathies humaines” team and the new IRCC project that should implement the translational research and especially the projects on molecular targets in hematological disease and animal models of diseases.

The lab is important for the training of hematologists coming from most of the Paris Hospital Hematology departments in addition to IGR (Trousseau, Mondor, Hotel Dieu/Saint Antoine) as well as other Universities Paris 6, 7 and 12.

Major scientific breakthroughs have been achieved in the field of myelo proliferative disorders and hematopoietic differentiation. This is also translated in the quality of rank A publications and patents (4 from which 3 are licensed).

The present director is clearly willing to help the new director in the management of the lab thanks to his knowledge of the research projects. He will help him combining his work at the IRCC together with U790.

The team leaders are involved in teaching but also adminsitrative functions at INSERM scientific committees and scientific council, asssociations and INCa.

The Université Paris 11 supports the ongoing efforts made by IGR through IRCC as well as the new managment of the lab.

The three teams have excellent expertise in the fields of hematology however they noticed that they need to support the emergence of team 1 as well as attract new groups to complete their expertise.

The interactions of the three groups are promising and should also be strengthened by interactions with the Necker hospital. Collaborations with the other INSERM teams would also be important to further develop their strategy.

4 • Specific appreciation team by team and/or project by project

Team1 : Microenvironment and self renewal of hematopoietic stem cells and leukemia initiating cells

This team includes 3 scientific staff, 1 technical staff, 2 post-docs, 3 PhD students, 2 Masters (M2) students. In the past 4 years, this group has studied the role of CXCR4 and its ligand SDF-1 in hematopoietic stem cell biology, megakaryopoiesis and chronic myeloid leukemia (CML). In a first project, they developed a mouse model to study the function of CXCR4 in fetal liver cells deficient for this receptor in a hematopoietic reconstitution system, as the $CXCR4^{-/-}$ mutation is embryonic lethal. Using this system, they found that CXCR4 plays an important role in controlling the distribution of primitive cells between the bone marrow and the circulation. In additional projects, this group evaluated the molecular mechanisms by which CXCR4 expression is regulated in different cell types. They found that RGS16 is a negative regulator of CXCR4 signaling during megakaryocyte differentiation. They also found that the nitric oxide (NO) pathway modulates CXCR4 expression in human $CD34^+$ cells, suggesting that NO plays an important role in trafficking. In addition, they investigated the regulation of CXCR4 in CML, and found that $p210^{BCR-ABL}$, which increases with disease progression, inhibits the SDF-1 chemotactic response in CML $CD34^+$ cells by altering CXCR4 signaling and expression. Lastly, $p210^{BCR-ABL}$ also appears to reprogram megakaryocyte progenitor cells into erythroid cells by repressing Fli-1 transcription. The scientific record of this group is excellent with high productivity in terms of publications (2004-2008 : 2 Blood, 1 Cancer Res, 2 Stem Cells, 1 Leukemia as primary authors ; 3 Blood, 1 J Immunol, 1 PloS One, 1 Haematologica as contributing authors).

They now propose to extend their findings in an ambitious program that aims to understand how CXCR4/SDF-1 interactions control normal HSC biology, how CXCR4 expression and function are influenced by its structure and its interactions with NO and CXCR7, and how CXCR4 plays a role in leukemic stem cell biology in acute myeloid leukemias (AML). The projects chosen have excellent future potential and are considered highly relevant for the field. However, given the competitiveness of this field, the committee has concerns that these projects are too wide-ranging for the present number of researchers involved. The committee recommends that the group expands to accommodate the projects, or focuses its energy on a reduced number of scientific questions.

MICROENVIRONNEMENT DE LA MOELLE OSSEUSE DANS LA BIOLOGIE DES CELLULES NORMALES ET LEUCEMIQUES

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

Team 2 : Normal and pathological erythropoiesis and megakaryopoiesis

This team includes 6 full-time + 3 part-time scientific staff, 3 technical staff, 5 post-docs, 7 PhD students, 5 Masters (M2) students.

The director of team 2 is a very well-recognized scientist with international leadership in the field of normal and pathological erythropoiesis, megakaryopoiesis and myeloproliferative disorders. The results obtained by this group these last years have a high impact for the scientific and biomedical community.

This team is going to be subdivided into two subunits:

Subunit 2a: This subunit is devoted, in line with previous achievements, to the study of hematopoietic stem cell emergence in the mouse embryo. This group has demonstrated in the past the presence of 2 independent hematopoietic sites (1 extra-embryonic and 1 intra-embryonic sites) within mammalian embryos and characterized with others the site, the phenotypic and functional properties of the intra-embryonic site homing definitive and multipotential hematopoietic precursors, the para-splanchnopleura/Aorta-Gonad-Mesonephros (p-SP/AGM) region. The new project relies on the identification of genes that may induce differential orientation of extra versus intra-embryonic hematopoietic precursors, through different strategies.

Despite the relatively recent arrival of the director of this subunit within the INSERM U 790, an intelligent use of the previous achievements and models by this director and its competences acquired in the past, allows the creation of this new subunit with 3 novel research projects that perfectly fit with the overall themes of Team #2. These projects need to be deeply supported.

Subunit 2b: The new project, in continuity to previously published data, is focused on normal and pathological erythropoiesis and megakaryopoiesis. Importantly, the group has previously shown that the mechanisms of polyploidization of megakaryocytes is related to a failure of late cytokinesis with an absence of myosin II concentration on the contractile ring linked to incomplete activation of RhoA/ROCK pathway. A detailed analysis of the role and regulation of myosin II and Rho GTPases during megakaryocitopoiesis using in vitro and in vivo approaches of KO mice is clearly a fascinating challenge of the project.

There is a good equilibrium between fundamental and applied research, in particular regarding translational projects on hereditary thrombocytopenia such as Wiskott Aldrich, Paris Trousseau and MYH9 syndromes.

ERYTHROPOIESE ET MEGACARYOCYTOPOIESE NORMALE ET PATHOLOGIQUE

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+

Team 3 : Chronic myeloid and lymphoid diseases; pathophysiology and translational research

This team is the largest of the unit including 3 full-time scientific staff, 6 part-time scientific staff, 6 technical staff, 6 post-docs, 8 students, 5 Masters (M2) students.

The director of team 3 is also the director of the unit. He is a world-wide recognized scientist with research work on molecular mechanism of differentiation apoptosis with a specific interest for the role of caspases in hematopoiesis.

The specific research of this team is focused on Philadelphia-negative myeloproliferative disorder, myeloproliferative myelodysplastic syndromes and mantle cell lymphoma.

The outstanding level of research of this group is illustrated by the discovery of JAK2 V617F as marker of myeloproliferative disorders such as Polycythemia Vera, essential thrombocytemia and primary myelofibrosis.

In addition, this team has recently discovered and identified a new gene tet-2 which seems to be a tumour suppressor gene playing a key role in the myeloid disorder. So, team 3 proposes to continue to increase the knowledge regarding the link between these two genes. A part of the work will be also focused on animal models to study myelofibrosis in the TPO high mouse model. New relevant animal models will be developed such as knock-in JAK2 and Tamoxifen

inducible Mice. A great part of work will be also focused on alteration of DNA stability either JAK2 dependent or JAK independent, for instance secondary to tet-2 inactivation.

The myeloproliferative/ myelodysplastic syndromes such as CMML will benefit by JAK2 story by the similarity of cytokine pathway activation on the M-CSF.

The research project concerning mantle cell lymphoma is less integrated in comparison to the other myeloid models but it should benefit from the expertise of the other Team 3 members.

Finally, the clinical and translational research of team 3 is obviously drawn from the research performed upstream for a long time and illustrates also the impressive results of this research and the outstanding level of this team.

MALADIES MYELOIDES ET LYMPHIODE CHRONIQUE

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+

5 • Appreciation of resources and of the life of the research unit

-Management :

Both researchers, technicians and PhD students were positive regarding the current management and appreciated the proposed evolution. Since the present director will stay in the lab, most of the ongoing projects will be supported by him. However, the new direction will help to have a better local integration since the new director will be in charge of IRCC and that hematology is one of the major projects of the campus. The work conditions are excellent with a good collaboration between researchers and PU-PH, MCU-PH and M.D.

-Human ressources:

The lab has a excellent score in the number of researchers, post docs and M.D and technicians. The support of the different platforms that are critical for their projects in animal models is being improved thanks to IGR and P11.

-Communication :

The organisation and communication within the lab are appreciated.

6 • Conclusions

— Strengths:

The lab has International and national recognition, and a long background in the field. The lab is among the international leaders in the field of Hematology research. It gathers most of the world major researchers in the field of stem cell research as well as identification of the genetic basis of hematological disorders.

— Weaknesses:

- The animal facility is poorly functioning and seems a permanent source of worries that may endanger/severely slow down research projects of team 2.
- Additional recruitment of young PhD/post-docs seems important in order to promote optimal development of the projects.

— Recommandations :

◦ The transposition of findings from mouse embryo to human embryo and ontogeny would be necessary to favour translational research for humans and valorise the work achieved.

◦ The three teams have excellent expertise in the fields of hematology. However they noticed that they need to support the emergence of team 1 as well as attract new groups to complete their expertise. The question of University position of the new director needs to be resolved.

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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+