Hémopathies myéloides : cellules souches, modèles précliniques et recherche translationnelle

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Myeloid Malignancies: Stem cells, preclinical models and translational research

Under the supervision of the following institutions and research bodies:

Université Paris 7 - Denis Diderot

Institut National de la Santé et de la Recherche Médicale

January 2013

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

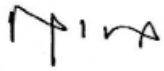
Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head



Pierre Glaudes

The president of AERES "signs[...], the evaluation reports, [...]countersigned for each evaluation department by the relevant head of department (Article 9, paragraph 3, of french decree n°2006-1334 dated 3 november 2006, revised).

Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).
This score (A+, A, B, C) concerned each of the six criteria defined by the AERES.
NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

Criterion 1 - C1 : Scientific outputs and quality ;
Criterion 2 - C2 : Academic reputation and appeal ;
Criterion 3 - C3 : Interactions with the social, economic and cultural environment ;
Criterion 4 - C4 : Organisation and life of the institution (or of the team) ;
Criterion 5 - C5 : Involvement in training through research ;
Criterion 6 - C6 : Strategy and five-year plan.

With respect to this score, the research unit concerned by this report received the following grades:

- Grading table of the unit: Myeloid Malignancies: Stem cells, preclinical models and translational research

C1	C2	C3	C4	C5	C6
A	A+	A+	A+	A+	A

Evaluation report

Unit name:	Myeloid Malignancies: Stem cells, preclinical models and translational research
Label requested:	UMR_S
Present no.:	UMR-S-940 Equipe 1
Name of Director (2012-2013):	Ms Christine CHOMIENNE (Equipe 1 from UMR_S 940)
Name of Project Leader (2014-2018):	Ms Christine CHOMIENNE

Expert committee members

Chair:	Ms Karin TARTE, Université Rennes 1
Experts:	Mr Daniel BIRBAUM, Université d'Aix Marseille
	Mr Bruno QUESNEL, Université de Lille
	Mr Marc RAAIJMAKERS, University Medical Center Rotterdam, Netherlands
	Mr Christian RECHER, Université de Toulouse (CNU representative)
	Mr Norbert VEY, Université d'Aix Marseille
	Ms Cécile VINDIS, Université de Toulouse (CSS INSERM representative)

Scientific delegate representing the AERES:

Mr Daniel OLIVE

Representative(s) of the unit's supervising institutions and bodies:

Ms Corinne ALBERTI, University Paris Diderot

Ms Chantal LASSERRE, INSERM

1 • Introduction

History and geographical location of the unit

The research unit "Myeloid Malignancies: Stem cells, preclinical models and translational research" emerges as an independent entity from the Research Center "Hematology, Immunology, and Therapeutic targets" created in 2007 and whose director is expected to retire at the end of 2013. This center is currently organized in three departments among which the Hematology department is proposed to be reorganized as a monothematic research unit. The team has welcomed recently new well-recognized clinicians and researchers that have strongly contributed to the design and organization of the new project and strategy.

The research unit is hosted at the Centre Hayem on the Hospital Saint Louis and benefits from research/clinic interfaces and facilities of the Institut of Hematology (IHU Paris Diderot) launched in 2010 including mouse facility, cell sorting/genomic/proteomic/imaging platforms, and biological ressource collections. Two new buildings are under construction on site and will host all these facilities.

Management team

The team director will be assisted by an operational team that will ensure daily organization including safety and security issues.

AERES nomenclature

SVE1_LS4 Physiology, physiopathology, medical systems biology

Unit workforce

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	5	4	4
N2: Permanent researchers from Institutions and similar positions	5	2	2
N3: Other permanent staff (without research duties)	4	3	2
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	1	1
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	8	11	11
N6: Other contractual staff (without research duties)	5	4	0
TOTAL N1 to N6	**28**	**25**	**20**

Percentage of producers	***83,33 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	6	
Theses defended	13	
Postdoctoral students having spent at least 12 months in the unit*	2	
Number of Research Supervisor Qualifications (HDR) taken	5	
Qualified research supervisors (with an HDR) or similar positions	13	10

2 • Assessment of the unit

Strengths and opportunities

- Clinically relevant questions,
- Strong embedding in clinical environment based on the integration of several clinicians and clinical biologists as project leaders,
- Recent arrival of new researchers bringing strong expertise and innovative tools and skills to the other projects,
- The projects are focused on connected diseases, and plan to use common state-of-the-art tools and approaches, providing a strong coherence between the research programs,
- Integration in National and European clinical and scientific networks,
- Good leadership of the candidate director,
- Integration within the St Louis Institut of Hematology, a highly attractive research pole, able to recruit international scientific and clinicial leaders and to create substantial opportunities for translating findings to patients,
- Strong implication in training of young scientists including coordination of an ITN FP7 project allowing the recruitment of foreign PhD.

Weaknesses and threats

- The low number of full-time basic scientists may represent a limit for the development of the five projects presented,
- The main common goal of identification and targeting of leukemic stem cells is critically dependent on the successful development of xenograft and iPS models, a challenging step not already fully achieved,
- Taken as a whole, this ambitious project lacks some clear hierachization of the experiments, and definition of a step-by-step working plan based on the identification of major milestones bridging clinical questions and basic science.

Recommendations

The development of five different projects targeting closely-related but distinct and heterogeneous diseases could be considered as a relevant option in this specific context based on the gathering of well-recognized clinical experts, but should be associated with a focus on the primary common question targeting leukemic stem cells. This may include prioritizing the building of the various models and should involve a clarification of the relevance of these models to answer the clinical questions (impact for patient treatment, understanding of leukemogenesis…).

3 • Detailed assessments

Assessment of scientific quality and outputs

The former team has obtained an international recognition in three fields: 1) identification of therapeutic targets in leukemias and solid tumors with a particularly significant contribution to the study of CD44 signaling and targeting in AML and to the understanding of the sensitivity/resistance of AML to retinoic acid; 2) identification of novel targets in chronic myeloid malignancies with very good translational research programs dedicated to polycythemia vera and juvenile myelomonocytic leukemia; and 3) study of stem cells for tissue repair, in collaboration with the cell therapy unit. Altogether, these projects were based on strong interactions with clinicians and provided findings with a great potential of transfert to the clinic. As an exemple, clinical demonstration of IFN-α efficacy against Jak2 mutated allele should be considered as a major breakthrough.

The team published 73 papers in dominant positions, including both scientific and clinical papers. The publication track record is thus good, including in particular 4 papers in Blood, 1 paper in JCO and several letters and full papers in Leukemia, but lack publications in general journals with high impact factor. When including collaborative work, the team was involved in more than 200 publications including J. Clin. Oncol., Blood, Nat. Med. In parallel to the departure of some contributive team members, one should note the very good publication records of the members that recently joined the team. Five patents have been filled.

Assessment of the unit's academic reputation and appeal

The academic reputation of team members is excellent, including scientists and clinicians. The team leader is a world class researcher, regularly invited to give talks in international meetings, organizing every year meetings or workshops for the European Association of Hematology (EHA), and coordinating national and european networks, in particular the Ile the France Cancer Stem Cell network and an ITN FP7 Marie Curie network. In addition, several clinical PI are considered as key opinion leaders in the field of myeloproliferative disorders and are strongly involved in national and international clinical networks. The unit succeeded in recruiting good to very good researchers in the past 4 years. These recruitments constitute a strong added value to the project in term of feasibility and reveal the team attractiveness as well as a good support form local institutions.

Assessment of the unit's interaction with the social, economic and cultural environment

The team has long-lasting implication in the development of clinical trials and has signed several contracts with pharmaceutical companies, including two CIFRE PhD fundings. As already mentioned, they registered several patents. In addition, some team members have been involved as experts in CNRS or Inserm scientific committees, Agence Nationale de Sécurité des Aliments or Inserm Institutional Review Board and the team leader is member of the executive board and president elect of the EHA. One start-up was created on immunotherapy combinations (winner of concours OSEO in 2008).

Assessment of the unit's organisation and life

The unit governance is being recognized by all staff members as performant and collegial with a good internal communication. A strong reorganization effort has been performed to integrate the new projects and new researchers and to share tools and expertise, based on regular common lab meetings. Emergence of autonomous projects and PI is clearly encouraged as underlined by the organization of the unit in small research groups coordinated by one or two senior researchers. Members of the unit who are MD/PhD smoothly combine working within the unit with clinical and laboratory duties and consider this organization as a chance.

Assessment of the unit's involvement in training through research

Involvement in teaching and training through research is clearly a major component of the team activity which contributes to the training of both medical and scientific students. The team leader, previously head of the Doctoral School in Hematology at University Paris Diderot, is now responsible of the Hematology Section of the Doctoral School B2T (“Biologie et Biotechnologie”) where team members coordinate some training modules. She coordinates an ITN FP7 network and the team welcomes regularly foreign students.

13 PhD theses were defended since 2007.

Assessment of the five-year plan and strategy

Overall, the scientific project is meaningful, ambitious, and carries great relevance both clinically and scientifically. It comprises 5 main axes dedicated to leukemic stem cell identification and targeting in various myeloproliferative and myelodysplastic syndroms. Development of xenograft models in these heterogeneous diseases is risky and internationaly competitive but is essential to build a program with long-term viability and strongly benefits from the recruitment of an expert investigator that positively impacts on the whole unit strategy. In addition, development of alternative 3D scaffold approaches will certainly bring some interesting results waiting for the completion of xenograft program in MDS. The projects on polycythemia vera and juvenile myelomonocytc leukemia are driven by internationally recognized clinicians and clinical biologists and could probably benefit from a more in depth definition of the direct relationship between basic research and clinical questions. The former team has obtained an international recognition through its productive work on CD44 signaling and targeting. A reorientation of this project, based on the hypothesis of a crosstalk between CD44 and PLZF, is proposed, owing to the recruitment of a young researcher with a strong molecular background. Finally, the DNA vaccine program, even if less connected to the rest of the project, relies on a long-lasting expertise in the field and represents an effective association of basic and translational research which opens to non-academic world.

4 • Conduct of the visit

Visit date:

Start: 24 January 2013 at 8:30 AM

End: 24 January 2013 at 5:15 PM

Visit site:

Institution: Hôpital St Louis, Institut Universitaire d'Hématologie

Address: Centre Hayem

Conduct or programme of visit:

The visit began at 8:30 AM by a meeting of the committee with the AERES representative. The futur director presented the major achievements of the previous team, as well as the overall scientific project and the general strategy of the new research unit for the 5 next years. The 5 PI presented thereafter their specific projects before a short discussion with the visiting board. After a first door-closed debriefing, the committee then split in 3 subgroups in order to meet sepearately researchers, PhD students/post-doctoral fellows, and technical and administrative staff. Finally, after a discussion with institutional representatives and with the team leader, the committee met for final debriefing and drafting the report. The visit ended at 5:15 PM.

5 • Statistics by field: SVE on 10/06/2013

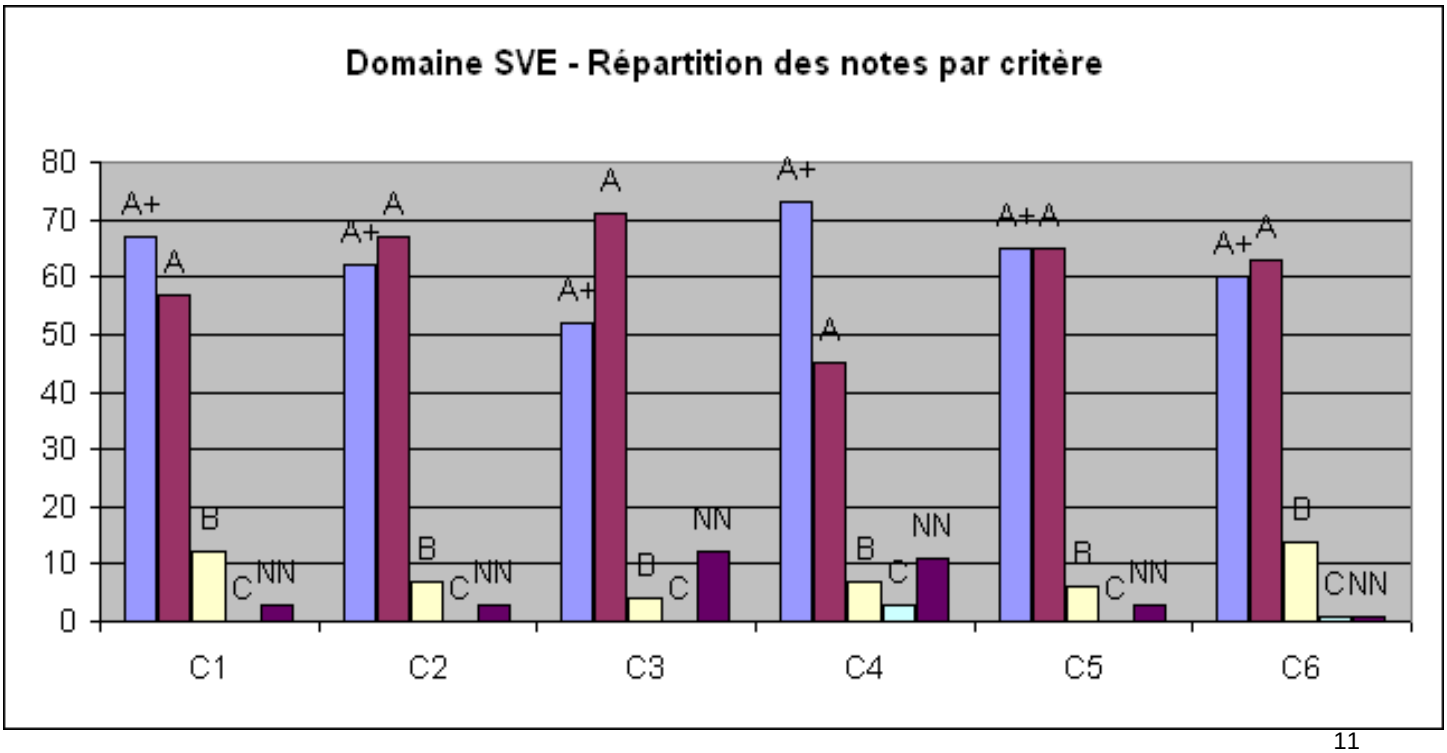
Grades

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	67	62	52	73	65	60
A	57	67	71	45	65	63
B	12	7	4	7	6	14
C	0	0	0	3	0	1
Non Noté	3	3	12	11	3	1

Percentages

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	48%	45%	37%	53%	47%	43%
A	41%	48%	51%	32%	47%	45%
B	9%	5%	3%	5%	4%	10%
C	0%	0%	0%	2%	0%	1%
Non Noté	2%	2%	9%	8%	2%	1%

Histogram



6 • Supervising bodies' general comments

université PARIS DIDEROT PARIS 7

Le Président

P/VB/RL/NC/YM – 2013 - 113
Paris, le 25 avril 2013

M. Pierre Glaudes
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

S2PUR140006425 - HEMOPATHIES MYELOIDES: CELLULES SOUCHES, MODELES PRECLINIQUES ET RECHERCHE TRANSLATIONNELLE - 0751723R

Monsieur le Directeur,

Je tiens en premier lieu à remercier les membres du comité de visite de l'AERES pour la production du rapport sur la situation de l'UMR 676 « Myeloid malignancies : Stem cells, preclinical models and translational research »». Sur certaines des remarques constructives formulées par le comité, la directrice a apporté des réponses en formulant des propositions, en particulier sur les jalons et perspectives scientifiques.

Le comité a relevé le très bon niveau de publication, les contrats et brevets obtenus et une excellente visibilité au niveau national et international, ce dont je me réjouis.

Comme vous le mentionnez, l'intégration dans l'IUH contribuera sans aucun doute à l'attractivité de cette unité que l'Université, à la hauteur de ses moyens, et en association avec l'INSERM, soutiendra pour le prochain contrat.

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

Vincent Berger

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Equipe 1 Département d'Hématologie : Professeur Christine Chomienne
« Cibles moléculaires et voies de signalisation intégrées des leucémies »

D2014-EV-0751723R-S2PUR140006425-003228-RT
Réponse: Erreurs factuelles (pas de corrections)
Réponse: Observations de portée générale

Paris le 9 avril 2013,

The members of the future research team have read the comments of the AERES visiting committee and thank them for their evaluation, quality of the report and thorough analysis of the future project. They are grateful to the AERES visiting committee for their positive feedback and very helpful comments that will certainly help them improve their project. The AERES visiting committee recognized that the common goal (past and future) of all the researchers is translational research in the diseases and pathways in which they have acquired international recognition. All researchers of the team thank the AERES visiting committee for their recommendations to improve the management by better prioritization of the selected models.

Strong networking of the researchers of the team, both at the clinical and fundamental research level, has been instrumental in the choice and development of these models. The Scientific Advisory Board (Christopher Bunce, Scientific Director of the Leukemic Lymphoma Research Fund, UK ; Christian Buske, Director of the Institute of Experimental Cancer Research at the Cancer Comprehensive Center, Ulm, D ; and Robert Kralovics, Research Center for Molecular Medecine of the Austrian Academy of Sciences, CH) has also been instrumental in the choice and establishment of the necessary models for the project.

The team was aware of the difficulties of some techniques and in particular (IPS cells and xenografts for MDS and MPN, not yet established in the field). We thus acquired, since 2010, the necessary researchers, technics, equipment, platforms, networks and collaborations. We have now developed the in-house expertise for each model that will enable us to provide answers for the clinical needs of these diseases: -) two strong protocols allow us to study the myelopoiesis of normal and PV IPS cell lines and the analysis of the Interferon alpha sensitivity in these cell lines; -) engraftment of MDS and JMML patient samples has now been achieved for 9 out of 15 samples and one out of two samples (respectively) by the researcher of *Group Stem Cells.*

We are now able to prioritize as requested by the visiting committee the use of these models for each given clinical questions and provide a more adapted working plan. The milestones and Gantt Chart were presented in the proposal (Table B page 14) and have now been amended with the preliminary results obtained on IPS cells in PV and MDS/JMML xenografts.

From M1 to M18, *Group Stem Cells* & *Environment* will establish a robust MDS xenograft model while *Group stem cells and MPN* sets the basis of the MPN xenografts. From M18 to M36, the establishment of the MPN xenograft models should be feasible with the combined efforts of both groups. From M36 to M60, the groups will characterize the initiating cells of MDS and MPN with the xenograft models taking advantage of the "3D" scaffold and the confocal biphoton microscope to study the role of the cells of the microenvironment in these diseases.

From M1 to M36 *Group Stem cell signaling pathways* and *Group enhancement of antitumour responses* will continue the preclinical studies in the MDS and AML-MDS transgenic mice models and the analysis of pathways of self-renewal and stem cell maintenance in AML models. From M36 to M60, these pathways and targets will be validated in patient xenografts in all groups and diseases.

Last, the team agrees with the committee's comment that it will be important in the close future to recruit new scientists to strengthen our team. We have now fundings for two post-doctoral positions for MDS xenografts, and nanoproteomic monitoring in MPN and MDS patients. We applied for funds for a post-doctoral position for stem cell pathway signaling (ITMO environment and ANSES) as well as a post-doctoral position for the MPN group (Emergence, Ville de Paris and QNRF). We are, as also, noted by the visiting committee in the process of seeking tenure positions for two basic scientists, already present in the team.

Pr Christine Chomienne