Hématopoïese normale et pathologique

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on research units:

Normal and pathological hematopoiesis

Under the supervision of the following institutions and research bodies:

Université Paris-Sud

Institut Gustave Roussy

Institut National de la Santé Et de la Recherche Médicale - INSERM

January 2014

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

Department for the evaluation of research units

On behalf of AERES, pursuant to the Decree of 3 november 2006[1]*,*

- Mr. Didier HOUSSIN, president
- Mr. Pierre GLAUDES, head of the evaluation of research units department

On behalf of the expert committee,

- Mr Bernard PAYRASTRE, chair of the committee

[1] The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n ° 2006-1334 of 3 November 2006, as amended).

Evaluation report

This report is the result of the evaluation by the experts committee, the composition of which is specified below.

The assessments contained herein are the expression of an independent and collegial deliberation of the committee.

Unit name:	Normal and pathological hematopoiesis
Label requested:	UMR_S
Present no.:	UMR_S 1009 and UMR_S 985
Name of Director (2013-2014):	Mr Olivier BERNARD and Mr Eric SOLARY
Name of Project Leader (2015-2019):	Mr Olivier BERNARD

Expert committee members

Chair:

Mr Bernard PAYRASTRE, Université Paul Sabatier Toulouse 3

Experts:

Mr Ivan CRUZ MOURA, INSERM, Paris (representative of CSS INSERM)

Ms Katleen FRESON, University of Leuven, Belgium

Ms Catherine LACOMBE, Université Paris Descartes (representative of the CNU)

Ms Véronique MAGUER-SATTA, INSERM, Lyon

Mr Michael SIEWEKE, Université d'Aix-Marseille

Mr Radek SKODA, University Hospital Basel, Switzerland

Mr Norbet VEY, Université d'Aix-Marseille

Mr Paresh VYAS, Weatherall Institute of Molecular Medicine, Oxford, United Kingdom

Scientific delegate representing the AERES:

Mr Daniel OLIVE

Representatives of the unit's supervising institutions and bodies:

Mr Christian AUCLAIR (director of Doctoral School n°418)

Mr Eric AUGE, Université Paris Sud

Ms Laurence PARMANTIER, INSERM

Mr Eric SOLARY, Institut Gustave Roussy

1 • Introduction

History and geographical location of the unit

This Inserm research unit results from the merging of two former Inserm units located in the Pavillon Recherche of the Institut Gustave Roussy (IGR, Villejuif):

- the single team unit 985 entitled "tumor genetics" directed by Mr Olivier BERNARD and created in 2010;

- the unit 1009 entitled "normal and malignant hematopoiesis" directed by Mr Eric SOLARY, composed of 3 teams and created in 2010 from previous units (362 and then 790) headed by Mr William Vainchenker for 18 years.

Several fruitfull scientific collaborations have been established between the two units during the last 5-years contract and a position for the unit administration was shared. Three senior researchers (DR) coming either from other Institutes (Cochin, Curie) or from other Inserm unit of IGR (U 749) will join the project unit.

One of the goal of this fusion was to associate groups developing complementary research lines on molecular bases of normal and pathological hematopoiesis both in humans and experimental models. In its new configuration this unit will be composed of four teams:

- team 1: "Early steps of hematopoietic transformation" (director: Mr Olivier BERNARD & Ms Virginie PENARD-LACRONIQUE);

- team 2: "From hematopoietic stem cell to megakaryocyte" (director: Ms Hana RASLOVA);

- team 3: "Genetics and models of childhood leukemia" (director: Mr Thomas MERCHER);

- team 4: "From hematopoietic stem cell to myelomonocytic differentiation" (director: Mr Eric SOLARY & Ms Françoise PORTEU).

A call to recruit a junior group was launched at the level of IGR and the selected candidat obtained an ATIP/Avenir position to join IGR in 2014. This emerging group working on Notch signaling and long non coding RNAs in hematopoiesis will be connected/affiliated to the new unit, particularly with team 1.

Management team

The current director of the Inserm unit 985, Mr Olivier BERNARD (DR1 Inserm) will be the director of the new unit for this 5-years Contract. Mr Eric SOLARY who was the director of the Inserm unit 1009 (a legacy of the unit created by Mr William VAINCHENKER 23 years ago) has numerous important duties (scientific director of IGR, Scientific president of ARC, etc) but will remain highly implicated in the direction to help the new director in the management of the unit. A steering committee composed of the group leaders will meet regularly to discuss administrative, organizational and scientific topics. A "unit committee" working on collective issues will be organized but the frequency of its meetings was not explicitly described in the application. Except for a part of the budget that will be shared to cover common expenses (equipment, cell culture, etc) each team will have its own budget policy. Scientific meetings to which all members of the unit are invited to attend are organized regularly.

AERES nomenclature

SVE1_LS2 Génétique, génomique, bioinformatique

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	9	9
N2: Permanent researchers from Institutions and similar positions	17	21
N3: Other permanent staff (without research duties)	10	9
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	19	17
N6: Other contractual staff (without research duties)	10	8
TOTAL N1 to N6	**65**	**64**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	24	
Theses defended	21	
Postdoctoral students having spent at least 12 months in the unit*	14	
Number of Research Supervisor Qualifications (HDR) taken	4	
Qualified research supervisors (with an HDR) or similar positions	21	

2 • Overall assessment of the interdisciplinary unit

Strengths and opportunities related to the context

1. The overall quality of the scientific production of U 985 and U 1009 is first-rate and the contributions of the different teams of these units is nationally and internationally renowned as attested by the high percentage of publications in high impact factor Journals (New Engl J Med, Cancer Cell, J Exp Med, J Clin Invest, Nature Commun, Blood, J Clin Oncol). The scientific output of the new researchers joining the unit is also excellent.

2. Efficient collaboration between U 985 and U 1009 have contributed to major discoveries improving our understanding and the management of hematopoietic malignancies: identification of major mutations and fusions (JAK2, TET2, ETO2-GLIS2, CSF3R), innovations for diagnosis, prognostic stratification or treatment.

3. The new unit gathers top level researchers and younger talented scientists making it one of the best research unit working on normal and malignant hematopoiesis. This unit is an asset to the education of the next generation of scientisit/clinicians in the field of hematology.

4. Most of the scientific projects are well-thought, address cutting-edge questions, are based on rigorous scientific processes, are highly competitive and innovative and are supervised by scientists with recognized leadership.

5. Seven very good platforms at the IGR (bioinformatics, imaging/cytometry, animal facility, omics, biobanking, immunomonitoring, translational research), grouped in a UMS, are made available to the members of the unit. Expansion of the animal facility is programmed (and urgent) and one of the lab scientist is developping a new IPScells/cell biology plateform.

Weaknesses and threats related to the context

1. Only few young researchers (2 CR2) have been recruited by U 985 and U 1009 over the last 5-year period and the balance between senior scientists and young scientists is not optimal for team 1 (5 DR/1PU-PH/0 CR). In this respect, the arrival, in 2014, of an ATIP/Avenir group that will be linked to this team goes in the right direction.

2. The experts committee noticed that although already well structured in several projects, the interactions with clinician hematologists (particularly at IGR) could be strengthened. The recruitment new PH in hematology to strengthen the hematology department of IGR is planned and should improve the potential of such interactions.

3. During the discussions, the experts committee noticed that the management procedures in the new unit should improve the structuration of the communication/information related to the scientific strategy and to collective issues.

Recommendations

The experts committee has been impressed by the overal quality of U 985 and U 1009 teams which have demonstrated their scientific excellence during the former contract and by the project of the future unit which has a high potential for significant discoveries with clinical implications. Considering the unit as a unique national resource, the experts committee estimated that integration of more clinicians (and MD students) in the research teams and formalization of the relationship with the hematology department at IGR and French cooperative groups should be recommended. Accordingly, the committee supports the attempt to recruit a PH to strengthen the hematology department of IGR.

Moreover, the unit should take advantage of its attractiveness to recruit young CR2 researchers, particularly in team 1. The experts committee encourages the recruitment of post-doctoral fellows from abroad with very good track record that would be eligible for CR position.

The experts committee has appreciated the synergies between the groups of the unit and encourages the director to foster the initiatives to develop transversal projects that are valuable catalyzer of the unit dynamics.

An effort shall be made to improve the sharing of information between the “steering committee” and the rest of the future unit, possibly by increasing the periodicity of the “unit committee”. In the same line of thinking, the experts committee encourages the students and post-docs to get more implicated in the scientific animation of the unit.

3 • Detailed assessments

Assessment of scientific quality and outputs

U 1009 and U 985 cover several field of research from genetic to biological bases of normal and pathological hematopoiesis and are among international leaders in the field. Considering the intense international competition of these topics, the scientific output of the different principal investigators within both units and that of new researchers joining the new unit is truly remarkable. Publication track record is impressive both quantitatively (more than 180 in 5 years) and qualitatively (high percentage of high IF journals such as New Engl J Med, Cancer Cell, J Exp Med, J Clin Oncol, Nature Commun, Cell Stem Cell, Blood). For most publications, the implication of the unit's members is very strong. Several seminal discoveries published in excellent journals in biology (Cancer Cell, NEJM, J Exp Med, Blood) are the result of well-established collaborative work between the two units.

The research projects in the past are of excellent quality and have received important international recognition leading to a better understanding and management of hematopoietic malignancies. The identification of major mutations and fusions (JAK2, TET2, ETO2-GLIS2, CSF3R) resulting in readily applicable innovations for diagnosis (JAK2 in MPNs), prognostic stratification (MDS, CMML) or treatment (IDH). One of the strengths relies on rigorous scientific process starting from the study of normal mechanisms (e.g. megakaryopoiesis) on which hypothesis regarding malignant transformation mechanism can be made. In addition, the group has focused on the study of models, either "naturally occurring" such as rare familial or constitutional disease predisposing to leukemia (FPDs, DS etc) or in vitro/in vivo models they established, a strategy that has proved to be highly successful.

Assessment of the unit's academic reputation and appeal

Senior researchers have national and international reputations as leaders that is reflected in their roles in conferences (invited speakers and/or organization : EHA, ASH, AACR, etc.), grant bodies, membership of international hematological organizations, editorial boards of journals, implication as scientific advisory experts and/or project/journal reviewers and in the awards they have received (Prix FRM, Prix of the French Academy of Science, Prix of the American Society of Hematology, Prix Charles Oberlin, Prix SFH, etc). Several principal investigators are involved in or coordinate national research programs (INCa, ANR, ARC, FRM) and have important national and international functions (The current director is President of the scientific committee of Fondation ARC, scientific director of IGR and of Cancéropole Île de France; the future director is member of scientific committee of Inserm CSS2, of SFH, CHO and ESH; the first director of one of the unit is expert in hematology at ITMO and member of the scientific committee of SFH, LNCC, RITC, ASH; another team leader is member of the scientific committee of Fondation ARC and CHO).

Some younger investigators follow this path. One of the team leader has received the EHA Jose Carrera Award in 2009.

The presence of a number of post-doctoral fellows and the arrival of several well known researchers from other French institutes illustrates the attractiveness of the unit.

U 1009 and U 985 and the future unit are very important for the training of hematologists and the Université Paris-Sud (Paris 11) supports the ongoing efforts made to structure the new lab within IGR. Some principal investigators are also clinicians in addition to their research interest and are involved in biomedical programs.

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

Several members of the unit have contributed to documents for patients associations, and public information (local TV channels, videos, news papers). The diversity of disciplines makes this a very broadly oriented research unit in hematopoiesis that is able to perform truly translational research via collaborations between the different research teams and the clinical hematological departments at IGR and other hospitals. Important attention is also given to valorization of research findings (several patents) and collaborations with private companies.

Assessment of the unit's organisation and life

Outstanding staff that forms the backbone of this research unit have demonstrated great leadership of research units. Mr Olivier BERNARD is experienced in the direction of a laboratory. He is committed to the optimal organization of the new unit in order to fully benefit from gathering experts doing research in normal and malignant hematopoiesis and its structuring effect.

The organization of the unit is based on four independent groups, each headed by one (teams 2 and 3) or two team leaders (teams 1 and 4). The decision-making body is the "Steering committee" that includes the director and the group leaders. The administrative organization was already partly shared between U 1009 and U 985 before fusion.

During the meetings of the experts committee and the staff of Scientists, ITA and students/post-doctoral fellows, the comments expressed on the conditions of work and the scientific life were generally positive. However, the new organization being just set up, several members of the unit mentioned that the transmission of the information from the steering committee to the whole unit should be optimized.

The emergence of young investigators towards leadership is promoted in the new unit and confirmed by the emergence of 2 of them as leaders of team 2 and 3, respectively. The unit is expected to be reinforced by the new organization in 4 teams, the identification one of the group as a team, and by the joining of new researchers.

Assessment of the unit's involvement in training through research

21 students successfully defended their PhD thesis over the last 5-years period in the two units and many students obtained their Master 1 and 2, which is a good indicator of the good quality of the tutoring and training. The majority of the students published as first authors in journals with IF>8. The unit has a good organization to train PhD students (weekly joined lab meetings and frequent subproject meetings). Many staff scientists are implicated in formal taught courses (Faculty of Medicine Paris 11 and Paris 7 Diderot, European Master of genetics, M2R "Biology of blood cells" and European Master in life Science "Cell Biology of Cancer" of Université Paris 7 Diderot).

Assessment of the strategy and the five-year plan

This novel unit entitled "Normal and pathological hematopoiesis" is a fusion of the two previous INSERM research units 'tumor genetics' and 'normal and malignant hematopoiesis'. The experts committee found that this is a well-organized and very strong multidisciplinary research unit with a clear vision on research policy and strategy.

Overall (and individually), the research projects related to the molecular biology and genetics of normal and malignant hematopoiesis are excellent. They are highly competitive and innovative, dealing with cutting edge issues regarding myeloid malignancies. There is a high potential for significant discoveries in the different fields that are being addressed with major clinical implications.

Hypotheses are based on previous work of the groups and on the well-established collaborative work between the two ex-units. The models used or to be established are highly relevant. They support a research strategy that has proved efficient in the past. The projects developed by the scientists joining the unit are consistent with the expertise of the unit and are expected to reinforce the innovative contribution of this new unit to basic research but also the translation of scientific findings to the clinic.

The quality of the project guarantees that this unit will continue to play a leading role at the national and international levels.

4 • Team-by-team analysis

Team 1: Early steps of hematopoietic transformation

Name of team leader: Mr Olivier BERNARD & Ms Virginie PENARD-LACRONIQUE

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	3	4
N2: Permanent EPST or EPIC researchers and similar positions	6	6
N3: Other permanent staff (without research duties)	2	3
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	4
N6: Other contractual staff (without research duties)	4	3
TOTAL N1 to N6	**18**	**20**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	7	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	7	

• Detailed assessments

Assessment of scientific quality and outputs

Team members are internationally recognized for the discoveries of mutations in TET2 in patients with hematological malignancies (MDS, MPN, AML and more recently also lymphoid malignancies). They generated TET2-deficient mouse models that clarified the role of TET2 deficiency in the expansion of hematopoietic progenitor and stem cells. TET2 is one of the major epigenetic regulators of gene expression through its role in DNA de-methylation. The team has been consistently publishing in the top journals (NEJM, Cancer Cell, Blood).

Team members identified serum 2-hydroxyglutarate (2HG) as a tumor marker indicating the presence of IDH1 and 2 activating mutations at diagnosis or as a biomarker for minimal residual disease (J Clin Oncol). Their work with a pharmaceutical company on AGI-6780, an allosteric inhibitor of IDH2 (Science) is important and has a good chance to result in an important new therapeutic. AGI-6780 is currently being tested in a phase I/II trial at the IGR.

Assessment of the unit's academic reputation and appeal

One of the team heads is recognized worldwide as one of the leaders in the field of TET2 and related epigenetic modifiers in hematological malignancies. His standing is reflected by invited educational talks at international meetings (ASH, AACR, EHA) and membership in the EHA scientific committee. He was a member of the editorial board of Leukemia (2005-2010) and is an associate editor for the American Journal of Hematology (2012-present) and is member of the Inserm scientific committee CSS2. The other team head is similarly active in a manner commensurate with the stage of her career she is at. The attractiveness of the team is also illustrated by the arrival of 2 new senior researchers.

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

Within a very short time, the team has gone from discovering the TET2/IDH axis as a potential drug target, showing that 2HG is a useful biomarker, to an actual clinical trial with AGI-6780, with a pharmaceutical company as an industrial partner. The team has obtained support from the "Ligue Nationale contre le Cancer" 2009-2011 and 2012-2014 and contracts with ARC 2009 and Association Laurette Fugain 2010-2014. Mr Olivier BERNARD is involved in several national scientific committees of national institutions (SFH, CHO, ARC, La Ligue contre le Cancer) or European institutions (EHA).

Assessment of the unit's organisation and life

This is a key team for IGR both in the past 5 years and in the years to come. The team's work brings prestige to the institution and is attracting excellent co-workers (including an ATIP-Avenir group who will be in strong interaction with the team). The interactions within the team are well organized; there are regular team meetings with presentations of work in progress and discussion of recent publications (journal club).

Assessment of the unit's involvement in training through research

Members of this team teach in European Courses and have a good involvement in student's training through master organization and teaching. 5 students defended their PhD in the team over the last 5 years-period. One of the team head contributes to M2 courses at Paris 11 in Onco-Hematology and coworkers are involved in many teaching including Oncology-Hematology for medical students and in a Master in Lille (differenciation et oncogénèse).

Assessment of the strategy and the five-year plan

The team is addressing important questions in a competitive field. The core of the team will focus on epigenetic studies of normal and malignant hematopoiesis with a focus on TET proteins but also work on DNMT3A and IDH proteins. The team has mouse models that will make them competitive in the field. There is new emphasis on lymphoid malignancy in the proposal and good collaborations with experts in the field have been established and the preliminary data presented during the visit are very promising.

The work on IDH is important in particular the attempt to integrate the data on epigenetic regulation and "reading the metabolic state of the cell". This field is competitive but it is a measure of its importance. Overall, these projects are complementary and cover basic biology, mouse models and translational aspects with patient samples and clinical trials.

The team will be joined by a researcher, who will study cell transformation by SPI1/Pu.1.

Conclusion

- **Strengths and opportunities:**

- scientific excellence;

- international reputation;

- excellent translational aspects (from basic research to bed side);

- very good success in national funds raising.

- **Weaknesses and threats:**

The ratio between senior researchers (DR/PU-PH) and young scientists (CR) is unbalanced.

- **Recommendations:**

- take advantage of the attractiveness of the team to recruit young CR2 researchers;

- european funds raising encouraged.

Team 2 : From hematopoietic stem cell to megakaryocyte

Name of team leader: Ms Hana RASLOVA

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	3	3
N2: Permanent EPST or EPIC researchers and similar positions	6	6
N3: Other permanent staff (without research duties)	2	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	9	6
N6: Other contractual staff (without research duties)	3	1
TOTAL N1 to N6	**23**	**17**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	11	
Theses defended	9	
Postdoctoral students having spent at least 12 months in the unit	7	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	6	

• Detailed assessments

Assessment of scientific quality and outputs

This team produced an excellent research output, both quantitatively and qualitatively. They are represented by 6 PIs and have published 83 publications in 5 years (21 with IF >10 including Nat Commun, Cancer Cell, Leukemia, Blood, J Clin Oncol, J Clin Invest). The research of the previous team leader in the field of myeloproliferative neoplasms (MPN) is internationally recognized at the highest level. Productivity of the team has been constant at high level over recent years both in the field of MPN and in the field of inherited thrombocytopenias. The research of the team leader on Runx1, Fli1 and MYH9 in familial thrombocytopenias is well under way and looks very promising.

Overall, the research of team 2 covers both fundamental and clinical topics and makes very good and apparently seamless connections between these areas.

Assessment of the unit's academic reputation and appeal

Research from this team has an excellent visibility at the international level. The previous team leader received one of the highest honors of ASH, the Dameshek Prize in 2007, and the Jose Carrera prize from EHA in 2009. He was a chairman of the ASH subcommittee on 'hematopoiesis' and a former first editor of Blood. He received honors from EHA, la Ligue National Contre le Cancer, foundation AGF and others. He is actively involved in different national and international scientific networks (AERES, GrEx, ESH, ITMO).

The team leader has already made some important contributions to the field of normal and pathological megakaryocyte/platelet development that resulted in high impact publications, patents, invitations to major international meetings (Gordon Conference USA 2013) and some national awards (Grand Prix de l'Académie Française de Sciences 2012).

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

These projects are highly relevant for patient diagnosis, care and even ultimately for treatment. Team 2 identified the unique recurring and acquired JAK2 mutation responsible for myeoloproliferative disorders. This work led to an important patent and a diagnostic test. Moreover, JAK2 inhibitors from various pharmaceutical companies have been developed that are currently tested in clinical trials.

The previous team leader is involved in several national scientific committees of national institutions (ITMO, SFH, La Ligue contre le Cancer). He made videos for MPN patient associations.

Assessment of the unit's organisation and life

The scientific expertise was passed on with success from the previous team leader to the new team leader. Team 2 has clinical expertise added by three MDs to support their highly translational research topics. Collaborations are also foreseen with the other teams of this unit.

Assessment of the unit's involvement in training through research

All PIs in this team have been involved in the successful training of many PhD students and Master students. The PIs of team 2 have supervised 9 PhD theses within 5 years and 12 M2R. They are currently involved in the guidance of 5 postdocs and 11 PhD students. They also participate in teaching committees of different Masters (Université Paris 11 and Paris Diderot) and European Courses.

Assessment of the strategy and the five-year plan

The research topics of team 2 are in line with their previous studies as they focus on the understanding of the molecular control of megakaryopoiesis under normal conditions, in patients with thrombocytopenia (MYH9, ANKRD36, RUNX1), and during the ontogeny of hematopoiesis (ES/iPS derived MKs). The successful programs of this team also focus on MPN with important investigations related to the role of a newly discovered calreticulin (CALR) gene for MPN. There is no doubt that this team is capable to tackle the proposed aims, as presented in the different subprojects. This proposal will use very state of the art technology and the team has already gained expertise in many of the proposed technologies.

The proposed applications of iPS cells and differentiation technology is innovative and of importance for different projects of this team and is also of great value for other projects within the unit.

Conclusion

- **Strengths and opportunities:**

- scientific excellence;

- international reputation;

- very solid team well balanced in terms of organization, staff and projects;

- valorization with patents;

- very good success in national funds raising.

- **Weaknesses and threats:**

Long-term close interactions with clinicians on hereditary thrombocytopenia and on myeloproliferative disorders are not fully insured.

- **Recommendations:**

- develop interaction with hematologists at IGR;

- european funds raising encouraged.

Team 3 : Genetics and modeling of childhood malignancies

Name of team leader: Mr Thomas MERCHER

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1
N6: Other contractual staff (without research duties)	1	2
TOTAL N1 to N6	**4**	**5**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	1	

• Detailed assessments

Assessment of scientific quality and outputs

One of the groups (formerly a part of a team in U985) has made a major contribution into childhood AMK-Leukemia understanding with the identification of ETO2-GLIS2 fusion gene that is present in about one third of patients. This could be achieved thanks to a murine model generated in collaboration and also used for the evaluation of potential therapeutic agents such as DiMF and Aurora A inhibitors.

The second scientific axis of the group focused on normal megakaryocyte development. The role of a functional interaction between Ikaros/Notch/GATA1 was demonstrated. In addition, using a hESC model developed by team 2, gene networks at work during megakaryocyte development have been uncovered. The importance of this scientific project which has produced high-ranking publications (J Exp Med, Blood, Cancer Cell) fully justifies the identification of this group as a team as proposed for the future contract. A young researcher came back recently for

a permanent position in France (CR2) after his post-doctoral stay abroad. There are tight links and a fruitful collaboration established between major international laboratories in the field and the team.

Assessment of the unit's academic reputation and appeal

The group has gained a strong international reputation as illustrated by the Jose Carreras Young Investigator Award obtained by the team leader in 2009 (EHA) and the invitations to many international meetings. The team is well known nationally and internationally for the work on AMKL. The team leader is reviewer for several journals, international conferences and funding agencies (KKLF-UK, FWO-Belgium). The group is well-funded and obtained regularly major national grants and also a grant from EHA.

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

The team leader is member of the scientific advisory board of the Association Laurette Fugain. The team has several collaborations with international and national groups which led to many co-publications.

Assessment of the unit's organisation and life

This is an emerging team composed of 6 people:

- 2 researchers (CR1 and CR2);

- 1 postdoc;

- 2 PhD students;

- 1 technician.

Megakaryopoiesis and AMKL are scientific themes shared by the 2 researchers and they already co-published a paper in Blood in 2013, thus showing that they work closely together.

Assessment of the unit's involvement in training through research

The team leader teaches at the « Master Europeen des Sciences de la Vie », Université Paris 7. He supervised several students.

Assessment of the strategy and the five-year plan

The research project is excellent, based on the internationally recognized expertise of the group in AMLK. It continues and expends previous work on the AMKL model and on normal MK development. In vivo and in vitro (hESC) models, previously used and refined, guarantee the feasibility of this ambitious project.

With this strategy, this new team will follow the successful strategy elaborated by team 2 which has focused on rare conditions that predispose to acute leukemia in order to understand not only the mechanisms of transformation but also normal hematopoiesis and megakaryopoiesis. The project is well described; the strategy is clear with well formulated hypothesis.

The team will focus on functional role of ETO2/GLIS2 on leukemogenesis and will aim at deciphering the predisposing role of trisomy 21 on leukemic transformation in AMKL and ALL.

The second project will use ES and iPS to identify key genes regulating fetal hematopoiesis and test the working hypothesis that developmental context determines the fate of HSC.

Given the previous work done by the members of this emerging team, the models and the collaborations (both in-house and outside) which have been set-up, the presented project should be successful.

The major risk is related to the small size of the group for a huge amount of work to be done. Interactions with clinical groups on the AMKL project are poorly described and should be formalized in order to foster the transfer to the clinic of the team’s discoveries.

Conclusion

- **Strengths and opportunities:**

- scientific excellence;

- excellent scientific project;

- excellent collaborations.

- **Weaknesses and threats:**

The major risk is related to the small size of the group for a huge amount of work to be done.

- **Recommendations:**

- take advantage of the attractiveness of the team to recruit/attract postdoctoral fellows or researchers to investigate the different scientific questions of the projects.

- strengthen interactions with clinicians.

Team 4 : From hematopoietic stem cell to monocyte

Name of team leader: Mr Eric SOLARY & Ms Françoise PORTEU

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	3	2
N2: Permanent EPST or EPIC researchers and similar positions	5	7
N3: Other permanent staff (without research duties)	6	5
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	7	6
N6: Other contractual staff (without research duties)	3	2
TOTAL N1 to N6	**24**	**22**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	7	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	5	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	7	

• Detailed assessments

Assessment of scientific quality and outputs

The quality and the number of original papers published by this team during the last 5-years period indicates a remarkable ability to produce excellent work (128 publications, 14 with IF>10 as last author including 1 Cell Stem Cell, 1 J Clin Oncol, 8 Blood, 4 Leukemia).

The team members have reported new original findings concerning the role of the niche in the regulation of hematopoietic stem cells and its involvement in leukemia as regard to the response to soluble factors. The link with genetic and epigenetic alterations is likely to provide new cues in the understanding of both fundamental and pathological behavior of hematopoietic stem cells. Conceptually, new and interesting mechanism have been

discovered including oscillatory signaling, new scoring system with direct impact for clinical practice, new role of TPO protecting HSC from DNA damage.

Assessment of the unit's academic reputation and appeal

This team has gained a strong national and international recognition and is among the international leaders in the field of hematology research. The team has attracted an entire group from another institute in the past year that includes 2 researchers and students/postdoctoral fellows. Several members of the team are implicated in the organization of international meetings (EHA), are invited for oral presentations at international meetings (EHA, ASH, ISEH), are members of boards (4, including Leukemia) and are involved in reviewing in high quality journals (Nature Genetics, NEJM, JEM, etc). Members of the group also give international seminars and courses (~6/year).

The team leader is strongly involved in several scientific committees of national institutions (Direction of IGR, ARC, Canceropole Paris, IFR) and is involved in the advisory boards of multiple institutes and European programs.

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

The prognosis scoring system developed by the team is practice-changing. It is now routinely used in clinical practice to help clinicians inform patients of their likely prognosis. It thus constitutes a methodology of international importance in service to the public.

The use of TPO to protect HSC from radiation damage being patented by one of the team members would be extremely useful in radiation therapy.

The team has several industrial contracts for research applications (JAK2, CXCR4 inhibitors), contacts with journalists and science communications systems to the general public for Gustave Roussy, IFR54, Cancéropôle, Fondation ARC. Members of the team are implicated in the scientific council of BioIntelligence and in the “cellule virtuelle” program.

Assessment of the unit's organisation and life

The team leader has demonstrated great leadership in forming powerful alliances in management and scientific expertise. The arrival of an additional team leader shows strategic vision as she brings complementary expertise, her own excellent reputation and demonstrated skill of leading a successful team. The current team leader has brought innovation in the unit and institution by creating new platforms, by reforming recruitment and communication strategies, raising attractiveness and initiating or improving contacts to universities and other players in the scientific environment. He showed strong management skills in restructuring units/groups and associating researchers with their individual strong research background in a meaningful way and positive atmosphere.

Assessment of the unit's involvement in training through research

Team members participate in teaching committees (several Ph.D programs), teaching organization and teaching itself (including international courses: European school of Hematology). The team has a sustained activity in the training of many M2R, PhDs and post docs.

Assessment of the strategy and the five-year plan

The team will explore the molecular mechanisms that drive myelomonocytic expansion in homeostasis and in response to diverse acute/chronic inflammatory or genotoxic stresses leading in certain conditions to clonal myelomonocytic diseases. The role of CSF-1, CXCR4 and MPL receptors and their signaling in HSCs and in the myelomonocytic lineage will be investigated in detail. The projects on the role of genetic stability and epigenetic modification in chronic myelomonocytic leukemia (CMML) are highly innovative as well as the monocyte subsets phenotyping/genotyping in CMML.

The proposed project is ambitious, well supported by previous work, multifaceted and coherent. It appears feasible as all the competences, models and the required number of people is already in place to achieved the proposed objectives. The team treats its objectives thoroughly and exhaustively, approaching it from several angles, use modern technology and profit from available models and expertise within the team and the other teams of the unit.

Conclusion

- **Strengths and opportunities:**

- scientific excellence;

- international reputation;

- excellent project and expertise with translational aspects;

- experienced leadership and complementarity of the team leaders;

- permanent success in national funds raising.

- **Weaknesses and threats:**

Long-term close interactions with clinicians at IGR should be strengthened.

- **Recommendations:**

- the experts committee encourages the team leaders to stimulate and maintain efficient communication between the 7 researchers (DR/CR) of the group as they will have to harmoniously cooperate.

- collaboration with other Inserm units could be further developed.

- european funds raising encouraged.

5 • Conduct of the visit

Visit date:

Start:	Monday January 6th 2014 at 08.30 am
End:	Monday January 6th 2014 at 06.50 pm
Visit site:	IGR Pavillon de Recherche
Institution:	Institut Gustave Roussy
Address:	114 rue Edouard-Vaillant, 94805 Villejuif
Specific premises visited:	Inserm U 985 and U 1009, Institut Gustave Roussy, 94805 Villejuif

Conduct or programme of visit:

The visit was held at IGR pavillon recherche, the project was presented by the head of the unit, Mr Olivier Bernard, then the four team leaders presented their projects. The experts committee members then discussed with the representatives of Université Paris 11/Medical Faculty and Inserm as well as the scientific director of IGR. The experts committee members had a meeting with researchers, ITA (in the presence of the representative of ITA at Inserm CSS4), postdocs/students and with team leaders. The presentations were well organized and the experts committee had thorough and extensive discussion on most aspects of the projects as well as on the management of the research and its integration within IGR research campus.

08.30-09.00 am	Panel closed meeting
09.00-12.05 pm	Presentations: - overview – (Mr Olivier BERNARD) - team 1 – *Early steps of hematopoietic transformation* (Mr Olivier BERNARD) - team 2 – *From hematopoietic stem cell to megakaryocyte* (Ms Hana RASLOVA) Coffee Break - team 3 – *Genetics and modeling of childhood malignancies* (Mr Thomas MERCHER) - team 4 – *From hematopoietic stem cell to myelomonocytic differentiation* (Mr Eric SOLARY)
12.05-01.30 pm	Lunch break
01.30-02.00 pm	Meeting with the funding bodies (INSERM, IGR, Université Paris-Sud)
02.45-03.45 pm	Parallel meetings: - chercheurs ITA - étudiants, post-doctorants
03.45-04.10 pm	Discussion with team leaders
	Coffee Break
04.25-06.50 pm	Panel meeting
06.50 pm	End of the visit

6 • Supervising bodies general comments

UNIVERSITÉ PARIS SUD

Comprendre le monde, construire l'avenir®

Le Président de l'Université Paris-Sud

à

Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
AERES
20, rue Vivienne
75002 Paris

Orsay, le 20 mars 2014

N/Réf. : 63/14/JB/LM/AL

Objet : Rapport d'évaluation d'unité de recherche
N° S2PUR150007978

Monsieur le Directeur,

Vous m'avez transmis le 27 février dernier, le rapport d'évaluation de l'unité de recherche - - Hématopoïese normale et pathologique – n° S2PUR150007978 et je vous en remercie.

L'université se réjouit de l'appréciation portée par le Comité sur cette unité et prend bonne note de ses suggestions.

Vous trouverez en annexe les éléments de réponse de Messieurs Olivier BERNARD et Eric SOLARY, Directeurs de l'unité de recherche.

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

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Response to the AERES review (S2PUR150007978 - Hématopoïese normale et pathologique)

We first want to thank the committee for their time and their encouraging comments.
We agree with all the points that have been raised.
We will do our best to attract young researchers and reinforce the teams.
The interactions with and staffing of the hematological clinical department are also one of our concerns and we are actively working to improve these aspects.
Regarding the organization of the unit, we want to stress that the re-organizing process has just started. We are taking very seriously the committee's recommendations and we will make adjustments accordingly.