Research evaluation

EVALUATION REPORT OF THE UNIT

Normal and pathological haematopoiesis: emergence, environment and translational research

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Université Paris Cité,
Institut national de la santé et de la recherche médicale - Inserm

EVALUATION CAMPAIGN 2023-2024
GROUP D

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High Council for evaluation of research and highter education

In the name of the expert committee :

Lucas Jacques Waltzer, Chairman of the committee

For the Hcéres :

Stéphane Le Bouler, acting president

Pursuant to Articles R. 114-15 and R. 114-10 of the Research Code, the evaluation reports drawn up by the expert committees are signed by the chairmen of these committees and countersigned by the President of Hcéres.

To make the document easier to read, the names used in this report to designate functions, professions or responsibilities (expert, researcher, teacher-researcher, professor, lecturer, engineer, technician, director, doctoral student, etc.) are used in a generic sense and have a neutral value.

This report is the result of the unit's evaluation by the expert committee, the composition of which is specified below. The appreciations it contains are the expression of the independent and collegial deliberation of this committee. The numbers in this report are the certified exact data extracted from the deposited files by the supervising body on behalf of the unit.

MEMBERS OF THE EXPERT COMMITTEE

Chairperson:	Mr Lucas Jacques Waltzer, CNRS - Centre national de la recherche scientifique, Clermont Ferrand
Experts:	Mr Antonin Morillon, CNRS, Paris Mr Philippe Rameau, Inserm - Institut national de la santé et de la recherche médicale, Paris (representative of supporting personnel) Ms Marie-Bérengère Troadec, Centre hospitalier régional et universitaire de Brest - CHRU Brest (representative of CSS) Ms Valérie Ugo, université d'Angers (representative of CNU)

HCÉRES REPRESENTATIVE

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Ms Sabine Samacki, Université Paris-Cité
Mr Pierre-Emmanuel Rautou, Université Paris-Cité
Mr Claude Sardet, Inserm,
Mr Philippe Rataczak, Inserm
Ms Sabrina Sahnoun, Inserm

CHARACTERISATION OF THE UNIT

- Name: Hémopathies myéloïdes : cellules souches, modèles, recherche translationnelle
- Acronym: U1131
- Label and number: UMR1131
- Number of teams: 2
- Composition of the executive team: Mr Stéphane Giraudier

SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement
SVE3 Molécules du vivant, biologie intégrative (des gènes et génomes aux systèmes), biologie cellulaire et du développement pour la science animale

THEMES OF THE UNIT

The unit essentially focuses its research on normal and malignant blood cell production, with a strong valence toward translational and clinical research on different myeloid malignancies. Its research also covers some aspects of immune system tolerance, regulation of mRNA translation or p53 function in cancer.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The UMR11131 (Inserm–Université Paris Cité) 'Hématopoïèse normale et pathologique: Émergence, environnement et recherche translationnelle' is the continuation of a research team established by Dr C. Chomienne more than 25 years ago at the Hospital Saint-Louis. It occupies around 500 m2 on the Hospital Saint-Louis campus and the two constituent teams are located in two distinct buildings. The unit is headed by Dr S. Giraudier since its renewal in 2019.

RESEARCH ENVIRONMENT OF THE UNIT

The unit is affiliated with the Institut national de la santé et de la recherche médicale (Inserm) and with Paris university 'Université Paris Cité'. The unit is embedded in the Hospital Saint-Louis/Institut Universitaire d'Hématology (IUH), one of the largest European hospitals for haematological diseases. The IUH/IRSL (Institut de Recherche Saint Louis) provides access to genomics and imaging platforms as well as a pre-clinical platform facility. It is associated with a clinical investigation centre and a biobank.
The unit also has access to some high-end technological platforms located in other research units in Paris.

UNIT WORKFORCE: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	3
Maîtres de conférences et assimilés	2
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	3
Personnels d'appui à la recherche	13
Sous-total personnels permanents en activité	**22**
Enseignants-chercheurs et chercheurs non permanents et assimilés	5
Personnels d'appui non permanents	1
Post-doctorants	0
Doctorants	5
Sous-total personnels non permanents en activité	**11**
Total personnels	**33**

DISTRIBUTION OF THE UNIT'S PERMANENTS BY EMPLOYER: in physical persons at 31/12/2022. Non-tutorship employers are grouped under the heading 'others'.

Nom de l'employeur	EC	C	PAR
UNIVERSITÉ PARIS-CITÉ	5	2	5
Inserm	0	2	4
AUTRES	0	0	4
Total personnels	**5**	**4**	**13**

GLOBAL ASSESSMENT

Profile, resources, and organisation
The unit conducts various lines of research concerning the normal and pathological development of blood cells. It has a long and successful history in the characterisation of haematological malignancies and was joined for this contract by a team with a strong expertise in the molecular basis of immune tolerance, in TP53 and the regulation of translation. Its activity encompasses sound and original lines of fundamental research coupled with strong clinical applications, in particular in onco-haematology. The resources of the unit are very good to excellent: the two teams were very well funded and the unit has access to some well-established platforms through the IRSL. Its strong links with the Hospital Saint-Louis constitutes a major scientific asset. However, the premises need to be upgraded. The organisation of the unit is very good, with an operational management and a suitable set of measures to ensure compliance with most regulations. Although the general atmosphere among the different categories of personal seems very positive, the scientific animation – in particular interactions between the two constituent teams – and formal management of the unit level could be improved. Of note too, important renovations of the premises are required.

Attractiveness
The attractiveness of the unit is very good. In particular, the recognition gained through its success in national competitive calls for projects at the French level is excellent, with several grants from the INCa, ANR, Inserm Plan Cancer or charities. Given its training potential, the unit hosted a very good number of PhDs (13). It also contributed effectively to teaching, notably at the M2 levels. However, several permanent staff left the lab or retired and the unit did not attract many postdoctoral fellows or young staff scientists. The unit is very well recognised for its expertise in the field of myeloproliferative neoplasms, leading to many national and international collaborations. Team 2 also has a strong international standing thanks to its involvement in other research institutes in Europe (e.g. second lab in Sweden, establishment of the ERC-funded International Center for Cancer Vaccine Sciences in Poland), but it did not seem to benefit directly to the unit.

Scientific production
The scientific output of the unit is excellent both in terms of quantity and quality given the size and composition of the unit. The unit published more than 190 articles, including 42 publications directly attributable to research activities of the lab. The unit obtained very original results along its various lines of research, some of which were published in the best journals of their speciality. This includes discoveries about the role of senescence in myeloproliferative neoplasms (J Exp Med 2021) or the molecular mechanisms of immune evasion by Epstein Barr Virus (2 NAR in 2022). The unit is strongly involved in clinical research in the field of hemato-oncology, leading to many collaborative publications with other teams in France and abroad. The potential synergy between the respective expertise of the two teams could have been better exploited.

Contribution of Research activities to society
The unit's interactions with society are excellent. The unit obtained several contracts with pharmaceutical companies (Amgen, Genentech, Janssen R&D, Novartis…) and it is strongly involved in translational research in onco-haematology. Team 1 is involved in several clinical trials and team 2 filed two patents. Various members of the unit are involved in teaching and training. Interactions with the general public and/or patient organisations could have been better highlighted.

DETAILED EVALUATION OF THE UNIT

A – CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

"The previous report mostly recommended increasing the international standing of the unit (through an application to international grants and collaborations), to fully integrate the new team in the unit, and promote the interactions between the two teams".
While the unit continued to conduct excellent scientific projects, these recommendations were not fully met during this contract.

B – EVALUATION AREAS

Considering the references defined in the unit's evaluation guidelines, the committee ensures that a distinction is made on the outstanding elements for strengths or weaknesses. Each point is documented by observable facts including the elements from the portfolio. The committee assesses if the unit's results are consistent with its activity profile.

EVALUATION AREA 1: PROFILE, RESOURCES AND ORGANISATION OF THE UNIT

Assessment on the scientific objectives of the unit

The objectives of the unit are scientifically relevant, very interesting and original, but the unit lacks a clear overarching strategy or scientific vision as the two teams have limited interactions and common scientific grounds.

Assessment on the unit's resources

The unit's resources are very good to excellent. The two teams were very successful in obtaining competitive funding at the national levels. The platforms available at the Hospital Saint-Louis provide up-to-date expertise for an important fraction of the experimental work.

Assessment on the functioning of the unit

The overall functioning of the unit is very good, with a simple and effective organisation and a suitable set of measures to ensure compliance with most current regulations. The atmosphere in the unit seems very good to excellent for all the categories of personnel, but the scientific animation and formal management of the unit level could be improved.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

This small unit is devoted to the study of normal and pathological blood cell development. It has a long and successful history in the characterisation of haematological malignancies. Its recent objective covers some important topics in the field of chronic myeloid malignancies and immunological control of cancer, which are scientifically sound and clinically relevant. It is strongly involved in translational research, thanks to the intermingling of researchers, PhD students and clinicians, as well as to its association with the Hospital Saint-Louis IUH. Given the interests and expertise of the two constituent teams, the unit was in a very good position to investigate the role of P53 inactivation in myeloid pathology progression. It is also well positioned in the study of haematopoietic stem cell generation or translational regulation of gene expression.

Weaknesses and risks linked to the context

The scientific integration of the two teams seems limited, with little synergies between them.

2/ The unit has resources adapted to its activity profile and research environment, and makes use of them.

Strengths and possibilities linked to the context

One strength of the unit stems for the very good number of clinicians (5 PU-PH, 3 PH) that it hosts and the presence of many support staff (7). The unit also benefited from the expertise of five Inserm researchers (including 2 emeritus director of research).
The unit managed to obtain significant resources from competitive grants (~440k€/year, mostly through national grant agencies and charities), which represent around 75% of its budget and notably allowed to employ many support staff on short-term contracts (around 15). The support by the supervising body has remained stable since the creation of the unit (174k€/year since 2019).
The unit benefits from strong genomic and cell imaging platforms as well as a platform to perform state-of-the-art malignancy xenografts. It also established new services for iPSC, nanofluidic proteomics, confocal biphoton microscopy and epigenetic. Neighbouring institutes can provide further high-end technological platforms.

Weaknesses and risks linked to the context

Although the unit invested in some equipment (FACS, qPCR), it relies strongly on the Institut de Recherche Saint-Louis platforms and its capacity to support or enhance these technological platforms in terms of HR/services is not well established.
There was a high turnaround of staff during the contract with a reduction in permanent researchers, and clinicians, several of them working now as emeritus, which could jeopardise the unit's capacity to conduct ambitious projects.
The current state of the premises is worrying, with some health and safety issues that need to be addressed more effectively. Important renovations are required to reach acceptable working conditions.

3/ The unit's practices comply with the rules and directives laid down by its supervisory bodies in terms of human resources management, safety, the environment, ethical protocols and the protection of data and scientific heritage.

Strengths and possibilities linked to the context

The modest size of the unit favours a smooth management and the potential involvement of all the unit members. It appears to comply with the regulations of its supervising bodies in Health and Safety as well as for pre-clinical research, patient sample collection/use and other ethics or integrity issues. One H&S officer is present in the unit and ensures that the relevant procedures are in place notably for the training of newcomers.
The gender parity at higher levels of responsibilities is above average, although some women in leading position have retired during the contract and the two team leaders are males.
The unit has a level of scientific animation commensurate to its size, with weekly internal group meetings, monthly lab meetings with invited speakers or PhD/postdoctoral student presentations, regular Journal clubs, and seminar series through the IRSL.

Weaknesses and risks linked to the context

The modest size of the unit does not favour the development of a more ambitious program for HR management, mentoring for PhDs/postdoctoral students and young researchers or improvement of sustainable research practices.
The institutional procedures for harassment and psychosocial risk are not well publicised.
The 'conseil de laboratoire' does not seem to be well established, with the representative of all the different categories of personals (including support staff, PhD and postdoctoral students).
The scientific and social interactions between the two teams are not sufficiently developed.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

Overall, the attractiveness of the unit is very good. Given its size and composition, the recognition gained through its success in national competitive calls for projects is excellent. It also hosted a very good number of PhDs (13) and some postdoctoral students (5), but several permanent staff left the lab or retired. The unit benefits from genomic and cell imaging platforms as well as pre-clinical model mimicking human leukaemia. Its links with Saint-Louis Hospital are a major asset for the study of pathological samples.

1/ The unit has an attractive scientific reputation and is part of the European research area.

2/ The unit is attractive because for the quality of its staff support policy.

3/ The unit is attractive through its success in competitive calls for projects.

4/ The unit is attractive for the quality of its major equipment and technical skills.

Strengths and possibilities linked to the context for the four references above

The unit has attracted a very good number of PhDs (13). It also hosted five postdoctoral fellows; one of them was recruited as an Inserm researcher and another one as an Inserm engineer. Three foreign visiting scientists were hosted during the past contract, one of them became a postdoctoral student in the unit.
The unit had an excellent level of funding at the national level, which includes three ANR, three Inca, three Inserm Plan Cancer, as well as important grants from Fondation ARC, Fondation de France, Fondation Laurette Fugain or Fondation Leucémie Espoir. It also obtained some funding through partnership with international pharmaceutical companies (Kartos Therapeutics; Janssen R&D).
The former head of the unit, now an emeritus professor, has a very strong international reputation (vice president of EHA, VP board Horizon Europe on Cancer). A senior PU-PH has developed some valuable international collaborations. Several team members contribute to the national network on IFM.
The unit has a well-established expertise in the development of pre-clinical model to study leukaemia. It also benefits from strong genomic and imaging platforms at the IUH/IRSL.
It is embedded in the Saint-Louis Hospital/IUH, a major centre for haematological disorders, and thus has privileged access to rare pathological samples.

Weaknesses and risks linked to the context for the four references above

Most funds for the unit come from French institutions (ANR, INCA, Plan Cancer…) or charities (ARC, Fondation Laurette Fugain…) and no research grant was acquired at the international level.
Many permanent staff (technicians, engineers, MCUPH, PUPH) left the lab. The Inserm researcher recruited during this period left the unit. The other Inserm researchers have retired or will soon reach retirement age.
Some technical support staff have also left the unit (at least 3 IE?) and were not replaced.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The scientific production of the unit is excellent. It includes a very high amount of research and clinical publications, some of which in the best journals of their speciality, such as Blood, J Exp Med, Leukaemia, NAR or PNAS.

1/ The scientific production of the unit meets quality criteria.

2/ The unit's scientific production is proportionate to its research potential and properly shared out between its personnel.

3/ The scientific production of the unit complies with the principles of research integrity, ethics and open science. It complies with the directives applicable in this field.

Strengths and possibilities linked to the context for the three references above

Overall, the unit has published 43 research articles during this period, including eighteen as main authors, mostly in well-established and reputable international journals of the hemato-oncology, immunoloy and molecular/cell biology fields (Blood, Cellular Immunology, Haematologica, Life Science Alliance, NAR…). Of note, 34 of them (80%) were published in Open Access, which suggests a high level of commitment toward open science practices.
In addition, the members of the unit published a very high number of clinical research articles (>150). Several of these publications involved many members of the unit, including PhD students, and appeared in excellent journals (J Exp Med, Blood, Leukaemia…), reflecting the strong implication of the unit in French clinical consortia and its large network of collaboration as well as their capacity to develop excellent projects at the interface between clinic and fundamental research in haematology.

Weaknesses and risks linked to the context for the three references above

The large majority of the publications are not signed as the main author by members of the unit.
Some important actors in the unit are reaching retirement age; this could compromise the continuation of some original line of research.
The scientific interactions between the two teams have been very limited.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

Assessment on the inclusion of the unit's research in society

The unit contribution to society was excellent. The unit obtained several contracts with pharmaceutical companies and is strongly involved in translational research in onco-haematology. It is also involved in teaching and training students at different levels, notably with the development of a specific Master 2 curriculum and the hosting of interns and PhDs.

1/ The unit stands out for the quality and the amount of its interactions with the non-academic world.

2/ The unit develops products for the cultural, economic and social world.

3/ The unit shares its knowledge with the general public and takes part in debates in society.

Strengths and possibilities linked to the context for the three references above

The research lines of the unit are strongly connected with clinical research in onco-haematology. Several members of the unit have set up collaborations with various pharmaceutical companies (Abbvie/Genentech, Amgen, AOP Orphan, Kartos, Novartis…) to test therapeutic drugs or study myeloid neoplasms in iPSC, resulting in. They obtained ~550k€ of contracts with these companies.

Members of the unit also teach at the medical university as well as at biology students from UPC. The unit contributed to the development of the Master 2 'cell and molecular biology of haematopoietic cells'; it regularly hosts M1 and M2 students for internships and trained thirteen PhD.

Weaknesses and risks linked to the context for the three references above

The unit does not mention any activities in terms of outreach or communication toward the general public. Interactions with patient associations are also limited.

ANALYSIS OF THE UNIT'S TRAJECTORY

The unit will not be renewed. As part of the restructuration of Hospital Saint-Louis 'Institut de recherche', it is proposed to create a new 'Centre de recherche' which will gather 19 research teams into a single unit working along five axes (Haematology, Immunology, Dermato-oncology, Cell Biology/Virology/Cell Therapies, Data Sciences & Cohorts). An UMS will be set up to provide imaging, cell flow, genomics and pre-clinical models study technical platforms. The unit will also benefit from the support of various labelled programs (IHU Thema; Institut Carnot Opale; SIRIC InsiTu).
It is anticipated that Team 1 will join this future unit within the 'haematology' axis/department. It makes little doubt that Team 1 will fit very well with the research developed by the other teams belonging to this axis and could greatly benefit from this reorganisation. Team 2 should also join this unit, but it will merge with another team interested in immune tolerance. The scientific contour of this new team and its future leadership were not convincingly presented.
Of note, the committee was concerned that the organisation of the future unit seemed still ill-defined at the time of the Hcéres visit. Both teams are encouraged to play a proactive role in the definition of the future unit scientific contour and organisation.

RECOMMENDATIONS TO THE UNIT

Recommendations regarding the Evaluation Area 1: Profile, Resources and Organisation of the Unit

The committee recommends that the unit conforms to its institutional requirements concerning the organisation of a 'Conseil de Laboratoire' and adopts more effective measures to disseminate information about psychosocial risk and harassment.
It is recommended that the buildings hosting the two teams are refurbished to meet H&S requirements and international standards.

Recommendations regarding the Evaluation Area 2: Attractiveness

The committee recommends that the unit continues its effort to attract full-time researchers and renew its personals, taking full advantage of the ongoing restructuration of the Hospital Saint-Louis research centre to increase its international standing.

Recommendations regarding Evaluation Area 3: Scientific Production

The committee encourages the unit to maintain its excellent level of scientific production and the strong links between its fundamental and clinical axis of research.

Recommendations regarding Evaluation Area 4: Contribution of Research Activities to Society

The unit is encouraged to set up more actions toward the general public.

TEAM-BY-TEAM OR THEME ASSESSMENT

Team 1: Normal and pathological haematopoiesis: Emergence, Environment and Translational Research.

Name of the supervisor: Mr. Stéphane Giraudier

THEMES OF THE TEAM

Team 1 gathers four groups dedicated to translational research in myeloproliferative neoplasms (MPN), juvenile myelomonocytic leukaemia (JMML) and myelodysplastic disorders (MDS) with specific skills in fetal haematopoiesis, epigenetics and pre-clinical models.
Team 1 particularly focused on three main subjects: subclonal selection, senescence and its role in MPN and modelling of MPN.
The specific objectives of team 1 during the four years were to: (i) better define the impact of treatments on sub-clonal selections; (ii) better define the impact of additional mutations in MPN; (iii) model normal and pathological haematopoiesis; (iv) better define stem cell emergence marker and pathological development.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Team 1 self-evaluation report focuses its responses on weaknesses addressed by the previous Hcéres committee from April, 17, 2018. Briefly, the weaknesses of the unit consisted in obtaining grants, publications for PhD students, spaces and localisation of team 2 and recruitment of technical staff. These points are detailed in appendix 1 of the DAE and seem to have been considered during the 2017–2022 period. Importantly, more external grants have been obtained as showing in the financial document and a particular attention was paid to 1st author publications by PhD students, with recent examples shown.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	3
Maîtres de conférences et assimilés	2
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	3
Personnels d'appui à la recherche	9
Sous-total personnels permanents en activité	**17**
Enseignants-chercheurs et chercheurs non permanents et assimilés	5
Personnels d'appui non permanents	0
Post-doctorants	0
Doctorants	0
Sous-total personnels non permanents en activité	**5**
Total personnels	**22**

EVALUATION

Overall assessment of the team

The scientific productivity of the team is of excellent to outstanding quality, especially regarding translational and functional clonal studies that have direct clinical and therapeutic impact. The research focuses on myeloid malignancies development, combining fundamental, translational and clinical research.
The attractiveness of the team is excellent, with many national funding obtained. Senior researchers of the team are international leaders. The interactivity with society and pharmaceutical industries is excellent, supported by translational and clinical research of high output.

Strengths and possibilities linked to the context

The current research contract remains in line with the highly recognised expertise of the team in chronic myeloid malignancies, mostly MPNs (i.e. BCR-ABL1 negative myeloproliferative neoplasms) and JMML (juvenile myelomonocytic leukaemia). On these topics, team 1 conducts high-level research, including cognitive project and strong translational research. The team has a stable history, with research topics preserved over time, and permanent close collaborations with reference clinical teams and cooperative groups such as the FIM (France Intergroupe of Myeloproliferative neoplasms) of which one of the members is the president.
During the 2017–2022 period, team 1 highlights 47 scientific publications, essentially in high-level international journals (Blood, J Exp Med, Leukaemia…), which represents a median four papers/senior researcher. Of note, due to the presence of clinicians, the complete list of publications of the team is much larger and the team has an impressive list of excellent to outstanding publications, with ~200 publications over the duration of the contract. National and international collaborations are at the origin of more than 50 articles in the best oncology/haematology journals such as Lancet Haematology, Journal of Clinical Oncology, Blood, or of very good level such as Blood Advances, Haematologica, Leukaemia, British Journal of Haematology, and high-level genetics journals.
It should be noted productive national or local (St. Louis) collaborations, attested by high-level publications, and, at the international level, collaborations are effective in preclinical research with major teams, some in Germany or in England. In addition, team 1 develops multidisciplinary collaboration e.g. mathematical modelling of haematopoiesis.
The team also develops many partnerships with the pharmaceutical industry to test new drugs in MPN as well as with patients and patient associations. A quality-of-life study is currently under development in MPN.
The team projects are very well funded by recent grants from national contracts such as ANR (2019), INCa (PREV-BIO, Paediatric High Risk – High Gain, PHRC) or from charities and foundations (ARC, FMR, FRM, etc.)
Last, mentors of the team have been for a long time recognised as leader in Europe in research and medical sciences (president of the European Haematological Association – EHA – , leader of the FIM, French Intergroup of MPN). Senior members of the team each participate in their respective expertise field in consensus conferences of international experts, that results in the writing of editorials, reviews, and expert opinions reports.

Weaknesses and risks linked to the context

Despite abundant scientific production, partly supported by numerous collaborations with other clinical units and services, the team remains small, comprising relatively few tenured researchers and HU clinicians who are naturally not often physically present in the wet lab. Moreover, the announced retirement of several researchers risks weakening the team. Over the duration of the contract, there were few postdoctoral students (only 1). The financing grants were substantial but no European contracts were obtained.
The current organisation of the team comprises four distinct groups, two of which are likely to disappear with the departure of the researchers, unless their replacement is possible. This is particularly important in the case of tenured researchers who bring their expertise in fundamental approaches of haematopoiesis and in vivo models. There seems to be some potential for this with the arrival of a senior researcher.
The integration of research on MDS (excluding paediatric haematology) in team 1 and the nature of collaboration with clinicians specialising in MDS seems weak, without co-direction of Master or PhD students. It should be noted that only one of the involved clinicians will stay in the team in the future project.
In terms of presentation, the team did not take full advantage of the portfolio to highlight the quality of their work. Overall, not enough emphasis was placed on societal and patients outreach initiatives.

Analysis of the team's trajectory

The team projects will refocus on the concept of cancer stem cells/cancer initiating cells with a particular attention in the evolution of the chronic myeloid malignancies to acute secondary leukaemia that is of very poor prognosis and one of the fatal issues in these diseases.
The team hopes to address a number of key issues by studying interactions between different tumour clones and with non-tumour cells that are not restricted to competition but can include cooperation. The team will study the contribution of environment in the evolutionary course of precancerous clones and cancer emergence, or the contribution of cancer cell heterogeneity in treatment resistance and relapse.
They hypothesise that the clonal hierarchy and its evolution that we and others described recently in chronic adult or juvenile myeloid diseases (MPN, MDS JMML), as in normal haematopoietic cells is in part dictated by clone extrinsic mechanisms involving clone-environment interactions and that mechanisms independent of the cell-intrinsic 'fitness' of the clone could impact the clonal evolution.
Thus, the proposed future team will continue in its core research activity toward unravelling the understanding of chronic myeloid malignancies i.e. MDS and MPN with a more precise attention to the clonal evolution concept and its influencing parameters. It will focus on three objectives: (i) demonstrate and study the clonal selection due to environment modifications; (ii) develop new strategies to test the impact of senescence process in MPN and to test whether senolysis and senescence induction could play a role in MPN therapeutical approaches; (iii) modelling of MPN behaviour (natural history or history after therapies) using a collaborative approach with mathematicians.
It is an ambitious but feasible program that will capitalise on scientific achievements and might benefit from recently established collaborations (mathematical expertise, other experts research units), acquired and under revision grants and the Saint-Louis excellent scientific environment (Institute de Recherche Saint-Louis and IHU Thema).

RECOMMENDATIONS TO THE TEAM

Given its age pyramid, the team must ensure that it remains attractive and encourages the recruitment of senior researchers, technical staffs and PhDs/postdoctoral students. Good scientific results and existing collaborations should promote greater international openness, especially by obtaining European funding, which will also be a source of attraction for new researchers.
The project to integrate the different teams in Saint-Louis Hospital into a unique research centre is a great opportunity to amplify local collaborations for team 1. It will be necessary to ensure a good integration of research personnel and to take advantage of the new skills brought by the Institute.

Team 2: Team 2

Name of the supervisor: Mr. Robin Fahraeus

THEMES OF THE TEAM

Team 2 focuses on mRNA translation and its implication. Three major topics are investigated. First, they explore immune tolerance and translation by investigating a non-canonical mRNA translation event related to MHC I pathway. Second, they address unique cis-acting mechanisms of mRNA translation of Epstein Barr virus EBNA1 with potential implication for EBV-associated cancers. And finally, they study the role of MDM2 in controlling protein degradation or mRNA translation of protein such as P53.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Some recommendations and weaknesses were identified. Among them:
1/To fully integrate team 2 in the life of the unit.
This goal is not fully achieved as exemplified by the lack of numerous joint publications or joint activities.
2/ To relocate team 2 close to team 1.
This goal is not achieved either and has limited the interactions between the two teams.
3/ The shortage of senior research members in team 2 was highlighted.
This comment is still accurate.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	4
Sous-total personnels permanents en activité	**5**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	0
Doctorants	0
Sous-total personnels non permanents en activité	**0**
Total personnels	**5**

EVALUATION

Overall assessment of the team

The research topics of the team are excellent and highly original. Team 2 makes knowledge on mRNA translation and its consequences go far beyond the state-of-the-art. The scientific production is excellent.
The visibility of team 2 leader is outstanding; the team leader demonstrates a high capacity for establishing international collaborations and attracting international postdoctoral fellows. The team leader co-led an international centre for cancer vaccine sciences funded by the ERC and is also affiliated at two European Universities and Research Institute.

Strengths and possibilities linked to the context

Team 2 leader holds a leading position in the topic of TP53 mRNA structures and regulation, and non-canonical mRNA translation for setting up MHC class I immune tolerance. His visibility is also demonstrated by his diverse affiliations in other European universities (ex: Umea University, Sweden; Masaryk Memorial Cancer Institute, Brno, Czech Republic).

Team 2 leader has an excellent scientific output, with about more than ten publications (including reviews) per year in high/top journals. Most of those publications are from collaborative works with teams outside the Unit.
Three projects have been recently achieved and published in NAR in 2022 (n=2) and PNAS in 2023, and signed as last or second last author by team 2 leader. Both articles in NAR (2022) dealt with EBNA1 mRNA, EBV immune evasion and identified the regulation by EBNA1 of a nascent protein quality control pathway to regulate its own rate of synthesis. The article in PNAS (accepted in January 2023) showed that non-AUG-initiated translation of pre-mRNAs generates peptides for MHC class I immune tolerance.
Teams 1 and 2 share a publication accepted in late 2022 on TP53, MDM2 and MDM4 protein and mRNA expression in MDS and AML, demonstrating a collaborative effort (Br J Haematol 2023).

Team 2 has an excellent capacity to obtain European funds (IRAP funded by ERC, Cancer Research Foundation – Uppsala Univ, Czech Research Foundation, Swedish Research Council) and national research supports (ANR, ARC, Leucemie Espoir) making financial resources appropriate to achieve the research objectives of the team.
Team 2 has an excellent capacity to build national and international collaborations. Those collaborative works are successful with excellent joint publications (ex: NAR 2022).
Two patents are reported.

Weaknesses and risks linked to the context

The team workforce (tenured researchers) has not significantly evolved since 2017 raising doubt on its long-term sustainability.
The level of integration and synergy between team 1 and team 2 appears to be minimal.
Teaching activities, dissemination and outreach activities toward the general public or targeted audience other than the scientific community are poorly addressed.

Analysis of the team's trajectory

A new team (named ANIT) on immune tolerance applied to transplantation will be created by merging team 2, and two other team experts in organ transplantation and MHC-I presentation. This new team shows a great potential. The specific research program is, however, not sufficiently detailed. Robin Fahraeus will lead this new team.

RECOMMENDATIONS TO THE TEAM

The team should reinforce its workforce with permanent researchers on his specific research topics.
Robin Fahraeus, the team leader of the future ANIT team, will reach the age of retirement during the next mandate. His leave should be anticipated and a potential future team leader must be identified rapidly.

CONDUCT OF THE INTERVIEWS

Date

Start: 14 November 2023 at 8 a.m.

End: 14 November 2023 at 5 p.m.

Interview conducted: on-site or online

INTERVIEW SCHEDULE

8:00 – 8:15 Testing Zoom connections

8:15 – 8:30 Closed session Expert Committee (EC) – Scientific Officer (SO)

Assessment of the Unit, Scientific Plenary session

8:30 – 8:45 Presentation of the EC to the staff members by SO

8:45 – 9:15 **Presentation of the unit by Stephane Giraudier** (20 + 10 min questions)
Attending: EC, SO, all the unit members

Presentation of the teams

9:15 – 9:45 **Team 1: Normal and pathological hematopoïesis: emergence, environment and translational research (Stéphane Giraudier)**
(15 min presentation + 10 min questions)
Attending: Team members, EC, SO, director of the Unit
+5' private discussion with the PI; attending: EC +SO

9:45 – 10:15 **Team 2: Control of RNA translation and tumour cells (Robin Fahraeus)**
(15 min presentation + 10 min questions)
Attending: Team members, EC, SO, director of Unit
+5' private discussion with the PI; attending: EC +SO

10:15-11:00 Break – Closed session with EC and SO

11:00-11:30 **Researchers and professors**
Attending: Researchers except group leaders, EC, SO

11:30-12:00 Thesis students and post-docs
Attending: PhD students and postdocs, EC, SO

12:00-1:30 p.m. Lunch Break

1:30 p.m.-2 p.m. **Technical and administrative personnel**
Attending: Technicians, Engineers, Administrative staff, EC, SO

2 p.m.-2:30 p.m. **Meeting with the representatives of Inserm and University**
Attending: expert committee, representatives of Institutions, SO

2:30 p.m.-3:30 p.m. Closed session with EC and SO

3:30 p.m.–16:00 **Meeting of the Committee with the head of the unit**
Attending: Unit Direction, expert committee, SO

4 p.m. – 5 p.m. Meeting of the Committee – Finalization of the report (closed hearing)

PARTICULAR POINT TO BE MENTIONED

N/A

GENERAL OBSERVATIONS OF THE SUPERVISORS

Université Paris Cité

Le Président

Paris, le 19 février 2024

HCERES
2 rue Albert Einstein
75013 Paris

Objet : Rapport d'évaluation de l'unité **DER-PUR250024189 – Normal and pathological hematopoiesis: emergence, environment and translational research**.

Madame, Monsieur,

L'université Paris Cité (UPCité) a pris connaissance du rapport d'évaluation de l'Unité de Recherche **Normal and pathological hematopoiesis : emergence, environment and translational research**.

Ce rapport a été lu avec attention par la direction de l'unité, de la part de laquelle vous trouverez un courrier en annexe, le vice-doyen Recherche et le doyen de la Faculté de Santé d'UPCité, par la vice-présidente Recherche d'UPCité et par moi-même. Nous remercions le comité pour son travail d'évaluation.

Le doyen de la Faculté de Santé et moi même souhaitons souligner que l'unité se focalise essentiellement sur les pathologies myéloïdes et a une très forte valence translationnelle. Dans le cadre de la restructuration de la recherche au sein de la Faculté de Santé d'UPCité, cette UMR sera l'un des éléments constituants du futur centre de recherche unique sur le site Saint-Louis. Ce regroupement d'unités, marqué par de vraies restructurations au sein des équipes, a été accompagné par les tutelles et s'est appuyé sur l'avis d'un scientific advisory board international, avec pour objectif principal d'augmenter la visibilité de la recherche au sein d'UPCité et sur le site Saint-Louis en particulier.

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

Édouard Kaminski

Présidence

Référence
Pr/DGDRIVE/2023

Affaire suivie par
Christine Debydeal - DGDRIVE

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Inserm
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UMRS-1131

Hématopoïèse normale et pathologique : Emergence, Environnement et Recherche translationnelle
Pr. Stéphane Giraudier

Paris le 12/02/2024

Response to the HCERES EVALUATION REPORT OF THE UNIT:

Dear Madam, Dear Sir,

First of all, I would like to thank the committee and the reviewers of the unit.
Thanks to the committee to mention that the attractiveness of the unit is very good, that the scientific production is excellent both in term of quantity and quality and that the interactions with the society is excellent what are the main objectives of a research structure.

The committee pointed five main Weaknesses and risks:

1- "The premises have to be up-graduated"
2- "Institution process for harassment and psychosocial risk are not well publicized"
3- "Interactions between the two teams (of the unit) are not sufficiently developed"
4- "The "conseil de laboratoire" does not seem to be well established"
5- "Communication toward the general public/ interactions with patient associations are also limited"

Responses:

1- The buildings are not under the supervision of the unit director. These buildings belong to the university and discussions relative to the refurbishment to "meet the H&S requirements and international standards" have been done with the University for more than 6 years. (Already done by the director to the University during the past Unit). Unfortunately, no decision regarding the premises have been noticed to date to the unit.
2- The "conseil de laboratoire" is not active as reported by the director with the committee because the number of peoples in the unit is small and then, meeting with all the peoples working in the unit (students, staff, technicians, engineers, and researchers) are done every month. Of course, if the number of peoples working in each team increased drastically during the next few months, the "conseil de laboratoire" would be re-activated.
3- Concerning harassment prevention, publicity have been made according to the INSERM recommendations in the lab after the committee visit the lab.

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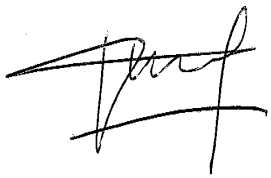
4- About the potential Synergy between the two teams, and as previously described by the director: Some collaborations have been performed, with one PhD student working in close collaboration with both teams, but we agree with the Committee that the synergy was limited. Based on this lack of full synergy and the recommendations of the HCERES committee, the two teams decided to not continue for the next unit to be in the same team.

5- Communication of the researchers with the patient associations have been done. (In particular with the Association "Vivre avec une NMP"), and S. Giraudier developed an app about patients own assessment of quality of life. This app is under validation and should be opened in the first trimester of 2024. This has been developed in collaboration with the association. However, this has been recognized as "clinical research" and not mentioned since it was not totally done in the unit perimeter. (which do not mean it is not done).

Bien cordialement,

Pr S. GIRAUDIER



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