Adaptateurs de signalisation en hématologie

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Signaling adaptors in Hematology

Under the supervision of the following institutions and research bodies:

Université Paris 13 – Paris-Nord

Institut National de la Santé et de la Recherche Médicale

January 2013

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

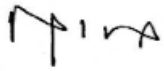
Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head



Pierre Glaudes

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

Grading

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

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

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

- Grading table of the unit: Signaling adaptors in Hematology

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

Evaluation report

Unit name:	Signaling adaptors in Hematology
Unit acronym:	ASIH
Label requested:	UMR_S
Present no.:	UMR_S978
Name of Director (2012-2013):	Ms Nadine VARIN-BLANK
Name of Project Leader (2014-2018):	Ms Nadine VARIN-BLANK

Expert committee members

Chair: Mr Bertrand NADEL, CIML, Marseille

Experts:

Ms Christelle GUIBERT, Bordeaux University (INSERM representative)

Mr Eric JENKINSON, Birmingham, United Kingdom

Mr Philippe KASTNER, IGBMC, Strasbourg

Mr Laurent MARTINY, Reims University (CNU representative)

Mr Bernardo Reina SAN MARTIN, IGBMC, Strasbourg

Ms Freda STEVENSON, Southampton, United Kingdom

Scientific delegate representing the AERES:

Mr Joost VAN MEERWIJK

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

Mr Charles DESFRANÇOIS, University Paris 13

Ms Marie Pascale MARTEL, INSERM

1 • Introduction

History and geographical location of the unit

The UMR_S978 was created in 2009, and is supported by INSERM, University Paris 13 and APHP (Hôpital Avicenne). This unit was the result of a fusion between the research group "Adaptors and regulation of haematopoiesis" led by Ms Nadine VARIN-BLANK (team 31 of U567 INSERM, Institut Cochin), and members of the EA 3406 University unit, which included bio-clinical staff from the "service d'hématologie biologique" (Université Paris 13, Hopital Avicenne, Bobigny), and more based on clinical studies. The motivation was to generate a translational continuum between fundamental and applied haematology based on experimental physiopathology of haematopoietic cells. The unit was created as a mono-team unit conveniently located on a single site (~325 m^2), UFR santé médecine biologie humaine (SMBH), University Paris 13-Hopital Avicenne, Bobigny, regrouping a staff of ~27-29 persons focusing on three main research themes:

1) Adaptors in early signalling

2) Adaptors in transcription

3) Application to human diseases

Management team

The proposed unit renewal is essentially structured similarly with a second direction term by Ms Nadine VARIN-BLANK.

AERES nomenclature

SVE1_LS6

Unit workforce

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	10	10	10
N2: Permanent researchers from Institutions and similar positions	4	4	4
N3: Other permanent staff (without research duties)	1	2	1
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)			
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	2	3	2
N6: Other contractual staff (without research duties)	1	1	1
TOTAL N1 to N6	**18**	**20**	**18**

Percentage of producers	***100 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	7	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit*	1	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	8	10

2 • Assessment of the unit

Strengths and opportunities

The unit represents a fusion between an Inserm team of cell biologists and members of a University-team including medical staff from a bio-clinical haematology department, both now located at the University Paris 13, UFR SMBH/Avicenne Hospital site. This fusion is a good strategic move, especially to expand studies of chronic lymphocytic leukaemia (CLL). There is an aim to develop further translational interactions by establishing an association with the department of internal medicine and the LabEx consortium to study auto-immune diseases in relation to CLL.

The unit produced a good scientific output (15/89 published articles with team members as senior authors, and one patent).

It contributes to a large number of collaborative projects, which account for nearly 90% of its publications. The ability to form partnerships is also underscored by the leading role played by the director in obtaining the INFLAMEX LabEx grant. The director is a co-coordinator for University Paris 13 of this national network of excellence on inflammatory diseases, allowing the unit to develop new projects on inflammatory diseases associated with lymphoid and myeloid diseases.

The unit has developed a trans-disciplinary research including mathematicians, chemists and physicists.

The unit has shown a good ability to secure funding from various sources (annual budget of 500-600 k€) with 25% of this amount from the EPST and 75% from other various sources. It has the resources to conduct its research.

It plays an active role in the teaching infrastructure of the Paris area and has shown a good record for attracting PhD students and getting fellowships for them.

It has strengthened its core research staff through the hiring of several people with positions as researchers or teachers.

Weaknesses and threats

The focus of the future research is in chronic lymphocytic leukemia (CLL) where international competition is very strong. An agile group will be needed to link the expertise of the two teams together and to establish effective and productive international and national collaborations.

Currently the unit functions essentially with a core work force of staff researchers and PhD students. Their effort should be pursued to hire more post-docs, who can bring valuable expertise, new ideas and techniques.

The number of authors from the laboratory named as first and last author is relatively low compared to the sum of articles resulting from more collaborative work. Although this translates great abilities to interact with other teams/topics at various levels (e.g. technical, expertise), this should not imply loss of focus.

The relative isolation of the unit at the Avicenne Hospital may prevent interactions with other research teams. This may have a negative impact on the training of students who may not be exposed to diverse scientific research. However, there are potentially interactive teams at the site and students apparently do travel to other sites within the Paris area for seminars.

Administrative management needs to be strengthened, since the unit appears to have only one part-time administrator (0.2 ETP).

Recommendations

The unit is still developing and requires time to consolidate its strengths. The chosen field of CLL is a good strategic move but intensely competitive internationally. If this is to be a focus of research, a new senior appointment of a full-time scientist with experience in B-cell biology is desirable.

The balance between students and mentors should be carefully considered. At present there are not enough full-time scientists able to guide the quite large number of PhD students, who are not sufficiently exposed to the field to represent a productive critical mass. Journal Clubs should be held in English and students should be encouraged to present posters at international conferences.

The director is doing a marvellous multitask job but she needs time to consider how to integrate CLL studies with the assays offered from the LabEx-funded technology. She spends too much time on administrative tasks.

The direct integration of the clinical and research staff is a unique opportunity, which should be reinforced at all levels (lab meetings, seminars, MD-PhD programs, etc.).

International positioning should be reinforced especially in the rapidly developing field of chronic lymphocytic leukaemia.

Attempts should be made to refocus the team's research and publication energy to the topics of the lab and attempt publishing in more generalist, high impact journals with lab members at a strategic place in the publication.

3 • Detailed assessments

Assessment of scientific quality and outputs

The team has followed up its previous work, which has centred on signalling pathways downstream of immune and cytokine receptors. It has characterized the role of the signalling molecules Lnk and APS in maintaining the homeostasis of myeloid cells in the mouse. It has shown that an interaction between Lnk and Jak2 (WT or mutant) is implicated in the progression of myeloproliferative neoplams in human. It has characterized novel functions of Vav1. It has studied the roles of the STAT1 and STAT3 transcription factors in cancer, and has developed decoy oligonucleotides as specific inhibitors of these proteins. It has begun to apply the techniques and expertise to B cell signalling. In chronic lymphocytic leukemia (CLL), it has confirmed data linking signalling through the BCR to disease progression and has analysed some of the intracellular pathways in CLL and in mantle cell lymphoma. The team has investigated mechanisms of retention of CLL cells in the lymph node and demonstrated a role for CXCR4 in this process. It has developed a flow cytometry-based method for biomarker analysis in CLL, for which it has obtained a patent.

In relation to the size of the unit, a high number of articles has been published with collaborators from both national and international teams in internationally peer reviewed and recognised journals. The high ranking of the IF highlights the scientific quality. In three years (2009 – 2012), 19/89 original articles have an IF > 10.

The team has produced 15 papers in which team members are senior authors (including 3x Blood, 1x Mol Cancer, 1x Haematologica, 1x Cancer Res, 1x Febs Journal, 1x BMC Cell Biol, 1x Plos One). The papers published in 2009/2010 show a decent citation record (Cancer Res 2009: 13 citations; Haematologica 2010: 10 citations; Blood 2010: 12 citations).

Assessment of the unit's academic reputation and appeal

The Director is part of numerous national and international organisations in charge of the attribution of funding's (ANR, German organisations, Europe organisations CEE-ERC, etc.).

Team members have participated in national and international meetings, to which they have contributed many abstracts.

The team is very successful in securing funds from a diverse set of national organisations (e.g. ARC, Fondation de France, Association Laurette Fugain) with 75% of their budget from other sources than EPST and it includes contracts with public associations and industries. The team leader is also coordinator of a large multi-team "Laboratory of excellence grant" which will provide 800 K€ to the team over 8 years. It is a participant in a European Marie-Curie Initial Training Network (ITN).

Some members of the laboratory are reviewers for well-known journals including J. Exp Med, Blood, J. Immunol, J Biol Chem, Oncogene, Plos ONE, etc., and are editors for Frontiers in Immunology and cancer medical science. They also actively participate in University committees (e.g. scientific council, department council), and they are part of selection committees for lecturers, professors and technicians.

The unit has recruited two young researchers; one CR1 INSERM in 2009 and three lecturers of whom one is a "chaire d'excellence INSERM/Université". One INSERM mobility joined the laboratory in 2012 showing the high attractiveness of the laboratory. Since the creation in 2009, the unit has thus considerably increased the number of researchers.

During the past three years, 18 undergraduates and 12 PhD students joined the unit for short or long periods of training including some foreign students (e.g. from Rome and Prague).

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

The research activity of the unit is devoted to translational research with the aim of finding biomarkers as well as new therapeutic tools for chronic haematological disorders. This applied research will have direct consequences to socio-economic and health issues.

The researchers have developed a platform to perform multicolour analysis of cells by cytofluorometry in order to better study signalling pathways in haematological disorders (a patent has been obtained for this process).

They are close to patient associations and they produced didactic documents to inform patients on CLL.

They have contracts with pharmaceutical companies to develop therapeutic targets (Becton Dickinson) and a student has a CIFRE grant.

Assessment of the unit's organisation and life

The Director performs management of the unit, with collegial discussion with the staff and/or their representatives for issues concerning life of the unit. The unit established clear and precise rules of governance, mentioning weekly scientific meetings and unit council-meetings three times a year where funding, administrative decisions etc. are discussed. This point facilitates the integration of new members of the unit including senior researchers as well as students. Lab meetings with all staff (researchers and clinicians) allow group dynamics and articulation of know-how between researchers and clinicians. Funds allocated to the unit are also managed in a collegial fashion.

The Unit's members are sensitized to good lab practices and a quality approach of the scientific research activity of the unit has been formalised with the written rules of procedure. Hygiene, safety, and ethical issues will follow legislation via the overseeing by a compliance officer.

The unit has established a platform of fluorescence-assisted functional analysis of signalling pathways (including cell-sorting, multicolour FCM, confocal microscopy), and benefits from research facilities of the site (animal facility, proteomics, tissue-teque, imaging), and access to a large cohort of patients from the Avicenne hospital. Close interaction with the 'Centre de Recherche Clinique' of the Avicenne hospital provides opportunities for developing translational research with pharmaceutical companies. It has also access to RMN and spectroscopy. The recently created IMAP13 aims to set up an imagery facility regrouping macroscopic (FCM, confocal imaging) and nanometric scale technologies (tip enhanced Raman spectroscopy system, TERS). Development of fluorescence imagery is on-going with mathematicians (Institut Galilée) in the frame of a FEDER program coordinated by the Unit's director.

Assessment of the unit's involvement in training through research

Several members of the Unit teach in science and medical degrees. They have developed a new master on inflammatory diseases. One of the team's members is in charge of two master programmes, one at the University of Paris 13 and a new Master associated with the LabEx. The Unit's director is a board member of the doctoral school "Galilee" and another member is associate-director.

Five PhD students have graduated during the evaluation period.

The laboratory participates in European network on haematological diseases with training of students and post-doc from different European countries. It has applied to join the Marie Curie international training organization without success but will try again.

Assessment of the five-year plan and strategy

Projects of the unit are coherent and well justified. They are in continuity with previous results and combine basic and clinical components. This translational research approach should improve and identify innovative ways of treatment of patients with different lymphoid and myeloid disorders.

The team addresses a number of fundamental and translational questions that they have divided into three main research axes.

Axis 1 concerns the functional study of key adaptor molecules (Lnk, Vav1). The Unit will (i) assess the effect of the Lnk mutations found in MPN in using myeloid cell lines as model systems and investigate the role of the functional domains of Vav1 in cell contact inhibition and tumorigenesis in non-hematopoietic cells; (ii) establish and compare the interactome of Syk, Lnk, APS and Vav1 in physiological and pathological cells; (iii) dissect the pathways that lead to NFAT activation in CLL and MCL and investigate the role of the Pi3K-PKD pathway in regulating CXCR4 levels in CLL; and (iv) investigate the role of Lnk in inflammatory pathologies. The work in this axis builds on the past and current work of the team and appears in many aspects to be the natural follow-up of current research. The emphasis on the role of the signalling molecules will greatly benefit from the close interaction with clinicians.

Axis 2 aims at studying the crosstalk between normal and pathological cells in CLL. The Unit will (i) study the role of chemokine signals in the retention of CLL cells in the LN; (ii) analyse regulatory B cells in CLL and their role in disease progression and concomitant auto-immunity; (iii) analyse the secretory pattern of CLL cells and determine its relationship with disease severity; (iv) analyse the inflammatory mechanisms elicited by infiltrating CLL cells.

Axis 3 aims at developing novel biomarkers and therapeutic strategies in haematological disorders. The Unit will (i) develop a flow cytometry assay to determine the level of activation of CLL cells that can be used routinely in the clinic; (ii) assess the relevance of a SNP for disease progression in myeloid disorders, and (iii) develop several strategies aimed at finding novel pharmacological inhibitors.

Altogether these aims are ambitious and well-focused around the theme of CLL. The team clearly has the expertise to carry out most of the proposed research. Some aspects are more novel to the team (*e.g.* role of B-regs) and may need collaboration with other experts.

Overall, the director has established a high reputation in the myeloid diseases research field. However, she is relatively new to B-cell malignancies and it will take time for the group to establish an influence in this field. Focus on CLL translational research has great potential thanks to the recognized clinical research expertise of the associate haematologist team. One issue is that the field of CLL has attracted, and is attracting, many investigators worldwide. The impact of signalling inhibitors in the clinic is changing the landscape of the disease and the team will have to take this into account.

4 • Conduct of the visit

Visit date:

Start: Wednesday, January 30st 2013 at 13:30

End: Wednesday, January 30st 2013 at 18:00

Visit site:

Institution: UFR SMBH, Paris 13 University

Address: 74 rue Marcel Cachin, 93017 Bobigny

Conduct or programme of visit:

13:30 - 14:00

Door-closed meeting: Committee members and AERES representative

14:00 - 15:15

Presentation by the head of the unit: past activity and projects

15:15 - 15:45

Meeting with representatives of the University Paris 13 and the Inserm

15:45 - 16:30

Three parallel meetings of committee-members and AERES representative with:

- PhD students and postdoctoral fellows
- engineers, technicians and administrative assistants (including technician CSS4)
- researchers with permanent position (except the unit's director)

16:30 - 17:00

Closed-door meeting of the committee and AERES representative with the unit's director

17:00 - 18:00

Closed-door meeting of the committee and AERES representative

Specific points to be mentioned:

Mr Laurent MARTINY was unable to participate to the site visit.

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

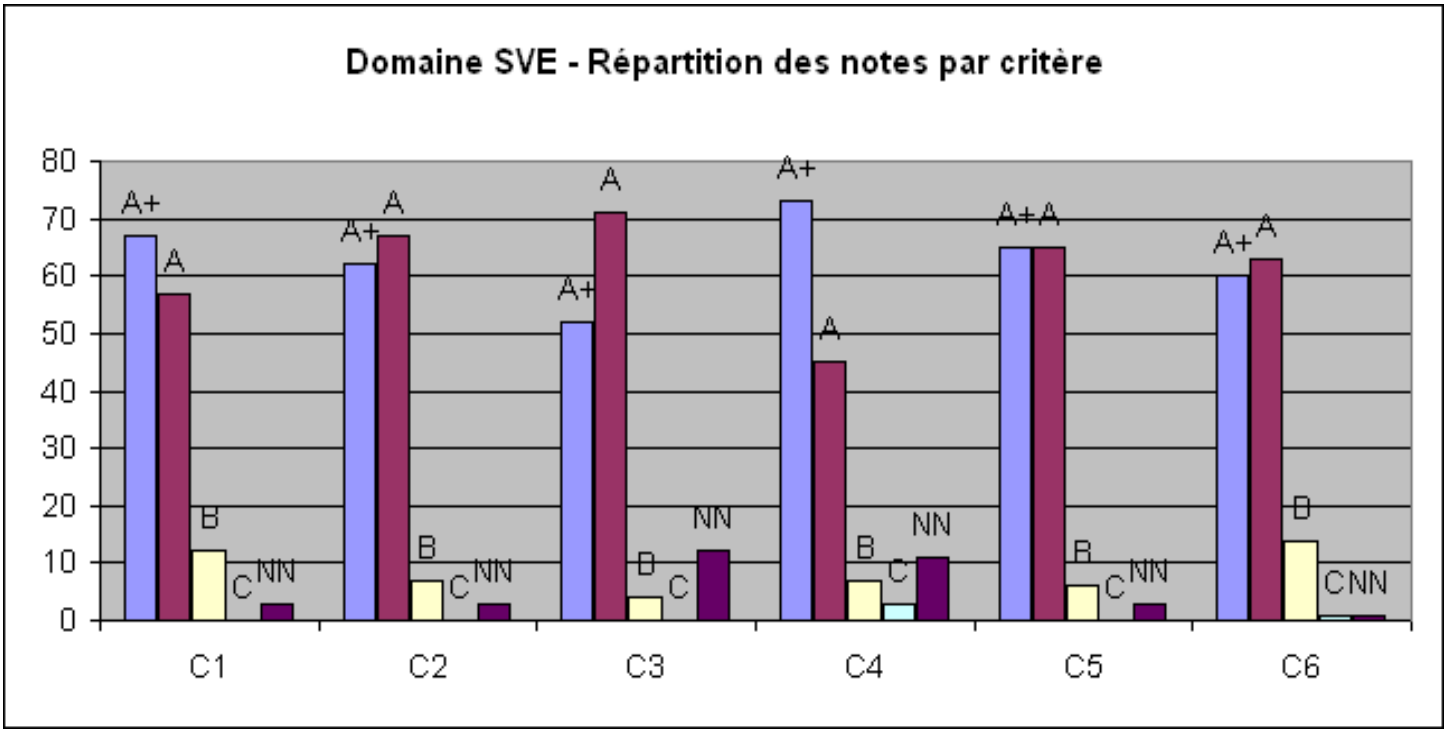
Grades

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

Percentages

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

Histogram



6 • Supervising bodies' general comments

UNIVERSITÉ PARIS 13 NORD

Villetaneuse, le 19 avril 2013

Le Président

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Observations générales sur le rapport AERES du laboratoire Adaptateurs de Signalisation en Hématologie (ASIH, U_978 Inserm – Paris 13)

L'université tient tout d'abord à saluer la qualité du comité de visite et de son rapport et se félicite de sa tonalité générale très positive.

L'établissement se réjouit de voir confirmées quelques très grandes qualités de ce laboratoire, en particulier dans les domaines de la production scientifique, de la réputation et de l'attractivité académiques et de la vitalité scientifique de tous ses membres et, plus particulièrement, de celle de sa directrice. Il se félicite également de voir validée l'approche réussie de recherche translationnelle issue d'un très bon couplage avec l'hôpital.

Nous prenons acte des quelques faiblesses pointées, notamment en termes de support administratif et de chercheurs postdoctoraux, et des recommandations constructives qui nourriront la poursuite des évolutions du laboratoire, dans un environnement international effectivement très compétitif.

Des réponses plus spécifiques du laboratoire, sur quelques points importants du rapport qui appellent des commentaires, sont données à la suite de ces observations générales.

Jean-Loup SALZMANN

Answer to the Report from the visiting committee

We thank the Committee for the positive comments on our Research Unit that has been created at the University Paris 13 in close proximity with the Avicenne hospital.

Please find below our comments to the various recommendations and points raised by the evaluation committee.

1) The committee has pointed out that: "The Signalling Adaptors in Haematology Unit is still developing and requires time to consolidate its strengths".
We acknowledge that the Committee raised this important issue since the Unit has been evaluated only three years after its creation *ex nihilo* in January 2009 and its effective move to its present location in June 2009. We have actively recruited and appointed new senior scientists since then, strengthening our research potential in the topics of the laboratory: 1 CR1 Inserm in 2009, 1 MCF "Chaire d'Excellence" in late 2009, 1 MCU-PH in 2010, 1 PU in 2011, 1 IR (Engineer) in 2012, 1 CR1 Inserm in 2012, and 1 MCF in late 2012. This active recruitment has also allowed bringing together complementary skills and expertise, and has resulted in the publication of 15 original articles with team members as senior authors. Furthermore, several new contributions of the Unit are currently in an editorial process, which will further consolidate our publication record.

2) We thank the committee for considering that working in the field of CLL is a good strategic move. Regardless of the competitiveness of this field, the team members have specific and internationally recognized expertise in deciphering signalling pathways, **which represents the core of the research focus of our Unit**. This is demonstrated by the development of our research in several haematologically relevant pathophysiological models in addition to CLL, including, for example, mantle cell lymphoma. Although well established, we believe that this aspect of our work, and our related results, have not been fully recognized and underlined in the AERES report.

3) The Committee expressed some concern regarding the potential isolation of the Unit. We believe that this is in contradiction with several other, positive statements expressed in the "Strengths and Opportunities" or "Assessments" chapters:

- At the local level: There is an exceptionally successful interaction in our Unit between basic scientists and bioclinical researchers. The position of the Unit in this particular geographic location makes possible unique and innovative functional studies that would not be possible at a distance. These projects permitted notably (*i*) the first demonstration of the implication of BCR-mediated signalling in CLL cell survival and disease progression (Deglesne PA et al., *Cancer Research* 2006, Vlad A et al. *Cancer Research* 2009, Le Roy C et al. *Blood* 2012) and (*ii*) the first demonstration of an active role of the Lnk inhibitor in myeloproliferative neoplasms (Simon C. et al. *Blood* 2008 and Baran-Marszak F. et al. *Blood* 2010).
Moreover, we also greatly benefited from the multidisciplinary character of the University site to initiate transdisciplinary research projects with mathematicians, chemists and physicists.

- At the Paris area level: The University is a founding member of the PRES SPC, and our Unit will certainly benefit from the fusion, in a near future, of the three main Universities in the field of Biology. Moreover, we are founding partners of the Labex INFLAMEX, a PRES SPC

Labex, and new collaborative studies with experts from the other teams (notably in B-cells oriented cellular immunology) are on going in this framework.

- Nationally and internationally: it is important to point out that the bioclinical haematology department is a national and European reference centre for several lymphoid disorders and is a founding member of the Intergroup on CLL as well as of the European network ERIC. This point is reflected by a number of invited conferences and participation to industrial boards for senior members of the team as well as important collaborative projects with 9 groups from foreign countries (UK, Canada, USA, Israel, Hungary, Russia).

4) The Committee has measured the strategic strength of the fusion of the founding laboratories; merging the basic research expertise in signalling modulation (including animal models) with the bioclinical expertise on haematological disorders. We believe that the group has already shown "agility" by establishing a growing national and international recognition on functional studies of haematological disorders. We will pursue this translational research keeping a specific focus on neoplasms for which we have pertinent physiological models. Our contribution to the Labex INFLAMEX will provide further expansion of our expertise in signalling towards other immune and inflammatory diseases. In this regard the Director has a longstanding recognition in the immune signalling field.

5) We acknowledge the recommendation of the Committee regarding the importance of exposing our students to national and international interactions. Concerning the balance between the number of students and their mentors, we would like to point out that the number of laboratory members with supervisor degrees (HDR) is rapidly increasing (currently 8 members of the Unit are habilitated giving a 1PhD/1 PI ratio, and 2 more members will defend before next summer) allowing, in fact, an efficient co-supervision between basic scientists and more clinically oriented mentors. Local interactions between PhDs are reinforced through the organisation of student-oriented seminars, and we strongly encourage and support the participation of our students to conferences (local or external) as well as to national and international meetings.

Dr. Nadine Varin-Blank
Directrice de l'U978 Inserm