



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

Section des Unités de recherche

Report from the visiting committee

Research unit :

Adapters of Cell Signaling in Hematology

University Paris 13



February 2008



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de recherche

*Le Directeur*

**Jean-Jacques Aubert**

February 2008



# Report from the visiting committee



## The research unit :

Name of the research unit : Adapters of Cell Signaling in Hematology

Requested label : UMR\_S

N° in case of renewal :

Head of the research unit : Mrs Nadine VARIN-BLANK

## University or school :

University Paris 13

## Other institutions and research organization:

INSERM

## Date(s) of the visit :

February, 4<sup>th</sup> of 2008



# Members of the visiting committee

## Chairman of the committee :

Mrs Naomi TAYLOR, Montpellier

## Other committee members :

Mrs Hélène MERLE-BERAL, Paris

Mr Ed PALMER, Lausanne, Switzerland

## CNU, CoNRS, CSS INSERM, (représentant INRA, INRIA, IRD.....) representatives :

Mrs Virginie PENARD-LACRONIQUE, Paris CSS INSERM representative

None of the CNU representative was available on the day of the visit

# Observers

## AERES scientific representative:

Mr François-Loïc COSSET

## University or school representative:

Mr Dominique BLADIER, Université Paris 13

## Research organization representative (s) :

Mrs Josiane POGGIOLI, INSERM-Scientific Evaluation Department

# Report from the visiting committee



## 1 • Short presentation of the research unit

The unit is composed of 38 individuals including :

- 2 full-time researchers (1 HDR ; 1 «publishing » lab member)
- 8 researchers with teaching duties: (4 HDR ; 7 are «publishing » lab members)
- 4 clinician-scientists (PH) (3 are «publishing » lab members)
- 6 PhD students
- 5 students completed PhDs between 2004-2008 ; average length of 3.5 years (2 articles/student)
- 2 lab members have been granted a PEDR
- 5 lab members have a HDR
- 8 publishing researchers (out of 10)

## 2 • Preparation and execution of the visit

The visiting committee met at the Medical UFR of Bobigny (SMBH) where the Director presented an overview of the unit. This was followed by short presentations given by 3 other senior scientists in the unit. All talks were followed by questions from the visiting committee.

The visiting committee then proceeded to the hospital laboratories (50m away) where there was a meeting with the medical staff of the Avicenne Hospital and the President of the University. Lunch was informal, allowing ample exchange with clinical staff as well as with students and post-docs. In the afternoon, the committee separated in order to meet individually with students and post-docs. Notably, all students and post-docs had prepared posters of their work (15 total). The visiting committee also visited the clinical laboratories and facilities associated with the proposed unit.

The committee then returned to the university (UFR) building to meet with university personnel and also visited the premises that will be renovated for this unit. The committee also had the opportunity to visit other core facilities such as the animal house.

The committee then debriefed, in the presence of the 3 observers, for approximately 1.5 hours before presenting preliminary conclusions to the research unit.

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

The unit represents a unification of the basic scientists presently working with the Director's INSERM team at Institut Cochin and the clinicians/teaching staff at Avicenne/U Paris 13 (most of whom are presently part of EA3406).

The clinicians associated with this unit are extremely dynamic and active, performing research that is directly applied to their clinical work; they have focused on chronic lymphocytic leukemias and mantle cell lymphomas, amongst others. They are already present at the University Paris 13 campus, but until now, they have not had any dedicated laboratory space in this campus. In addition to the research aspects of their work, these hospital-based faculty also play important roles in the initiation and evaluation of new clinical protocols, both at the national and international levels and specifically as regards B-CLL treatments and prognostic strategies.



The addition of basic scientists such as the Director and her colleagues to this unit promises to be an important addition to the University of Paris 13 campus. The clinicians and scientists involved in this unit have already collaborated during the past few years (shuttling between the Institut Cochin and the University of Paris 13) and the synergy between them is obvious. The achievements that they can reach together have huge potential and the AERES evaluation committee was impressed by the genuine interactions between the clinical and basic-scientist group leaders.

Finally, the visiting committee was impressed by the dedication and support of the medical school Dean and the University President with regards to the integration of this group on the Paris 13 campus. The university/medical school is obviously interested in fostering the development and success of this group and have translated these efforts into extensive lab space that will be renovated in the near future and changes in the animal house to promote the entry of new strains of mice as well as new types of technology that will be used by this group.

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

The proposed director of the new unit, is presently responsible for INSERM group 31 at the Institut Cochin. In the context of her group at Institut Cochin, the Director and colleagues have developed cellular and murine models aimed at studying the role of the Vav and Lnk/APS adaptors in the hematopoietic system. They are using these systems in order to characterize new partners of Lnk/APS and Vav. They are also attempting to identify physiological effectors of Lnk/APS in the signalosome downstream of the IL-7 and BCR receptors, amongst others. Their research during the past 4 years on the elucidation of the function of these adaptors has been very productive and has resulted in a good level of publication in specialty journals. The realization of their research in animal models has lagged behind but is expected to reach fruition in 2008. They now propose research to assess the roles of different domains of Vav and Lnk/APS by reconstitution of the hematopoietic system in their murine models and while this research was judged to be of high interest, it is very competitive and will require a high level of commitment at the senior scientist level. Finally, during the past few years, the Director has extended her basic studies on adaptor signalling to the elucidation of the roles of these proteins in pathological malignancies. It is this last research theme that forms the basis of the request for the present unit. Briefly, the groups of Institut Cochin and EA 3406 at Hôpital Avicenne (see below) have collaborated on BCR signalling in B-CLL cells and this research has resulted in the discovery of important information on the parameters modulating the survival responses of B-CLL in response to BCR ligation (published in *Cancer Research*). The continuation of these studies as well as projects aimed at elucidating the roles of Lnk and APS in myeloproliferative and lymphoproliferative disorders, respectively, as well as the characterization of Vav/Stat partners in transcriptional complexes (in hematologic malignancies) are the focus of collaborative studies to be performed in the context of this new unit. With regards to a clinically-applicable project that is achievable in the short term, the group is collaborating with BD-Biosciences to develop quantitative and qualitative analyses of diagnostic markers in CLL. The visiting committee judged the minor change in focus of the group, to directly study these adaptor proteins in lymphocytic and myeloproliferative disorders, to be highly positive and believe that this will be very beneficial for all involved. At the present time, it was judged judicious that the group continues its physiological studies of these adaptors in mice, but it remains to be determined whether the group can maintain a high level research on these related subjects.

The leader of the second group is the head of the Biological Hematology Service in Avicenne Hospital and a present member of the EA 3406 University of Paris 13 unit, located in the same site. She has focused her scientific activities on chronic lymphoproliferative disorders, with a special emphasis on chronic lymphocytic leukemia (CLL). The Hematology Service of this group leader is a reference center for several national and international therapeutic trials for CLL treatment, including participation in an EU FP7 network on *European Research Initiatives in CLL*. Furthermore, the team is a recognized international expert in cytometric analyses and has coordinated several European programs on minimal residual disease detection and ZAP-70 quantification in CLL. An important recruitment of patients from both the Biological and Clinical Hematology Services of the Avicenne Hospital (the director of the latter spoke with the visiting committee about his eagerness to join the proposed INSERM unit) has allowed the group to embark on fundamental and applied approaches aimed at elucidating pathological signalling in lymphoproliferative disorders. In this context, this leader has developed several projects based on the structural and functional analysis of the Vav and Lnk adapter proteins and their role in CLL with the group of the Director (see above). These exchanges have been very fruitful in fostering an improved understanding of the heterogeneity of CLL and have already resulted



in the co-authorship of several publications. In general, the collaboration between the fundamental and translational research profiles of the two groups has resulted in a good level of publications. The proposed research projects appear very promising and realistic, and justify the fusion of these teams in a single unit.

The leader of the third group has directed the EA 3406 unit at the University of Paris 13 since 2003. The projects developed by this team are focused on the roles of the Stat1 and Stat3 transcription factors in chronic lymphocytic leukemias, mantle cells lymphomas, and colo-rectal cancers (CRC), as well as their potential actions in chemotherapy resistance in CLL and CRC. In this regard, the group has also characterized potential prognostic markers in CLL (collaborating with group 2). More basic research axes are based on an understanding of the biological isoforms of Stat1 and Stat3 and the mechanisms via which Stat1 regulates IgG expression in B cells and mismatch repair in certain CCR. In an applied approach, they are pursuing a strategy to inhibit Stat activity using decoy oligodeoxynucleotides (ODN), a collaboration with two international teams who validate the ODN, and by an shRNA approach, in collaboration with other groups in Paris. The cellular models are in place and the translation to human tumor tissue is assured by the excellent environment of the biological hematology service (see above). It should be noted that the group has obtained numerous public (2006: AP/HP; 2004: contrat Legs Poix) and private grants (2005: ARC and Merck). The strong points of this team are the dynamic nature of the team members and their extensive international collaborations. The group is also a member of a French network on Stat activation. It is important to point out that the group has achieved an impressive research production, with publications in top specialty journals such as *Blood* and *J. Virol.*; this despite the fact that the vast majority of the group members also have extensive teaching responsibilities.

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

- Quality of the management :

The visiting committee cannot report on the overall management of this unit as the unit in its proposed form has not yet been created and currently represents individuals working in two independent institutions. That being said, the quality of the management of the core facilities that the visiting committee visited was extremely high, with a strong implication from top levels of the university and hospital. Additionally, the transfer labs that are already present within the hospital are functioning well.

- Quality of human resources :

As indicated above, the visiting committee was highly impressed by the interactions between the clinical physician-scientists and the basic INSERM/CNRS group leaders in the proposed unit. This appeared to translate into a very high level interaction with students and post-docs and those students with whom the visiting committee spoke were extremely positive about their experiences in the unit. This was also the case of post-docs who are presently commuting between research laboratory space at the Institut Cochin and the Hôpital Avicenne, in order to study various parameters in clinical samples. It is important to point out that the senior scientific/clinical staff in the proposed unit has extensive interactions and collaborations, nationally as well as internationally. They are very well respected by their peers and consulted on numerous occasions, at the clinical, basic research as well as industry levels. Of note, the hospital-based service associated with this unit collaborates with BD Biosciences, USA, testing new antibodies and cytometry advances in clinical samples. They have also developed new methods for better standardizing these techniques. In order to achieve the current and projected basic research projects, the visiting committee concluded that the unit will need to recruit at least one additional full time INSERM or CNRS scientist.

- Quality of the communication strategy :

There is a high overall level of interaction between the students/postdocs in the unit and the supervising scientists, both on a scientific and a career level. For example, PhD students in the unit have pursued international postdoctoral opportunities in collaboration with their host lab at the University Paris 13. Moreover, the group has coordinated an application for an FP7 Marie Curie training network grant for which they were highly ranked but not funded, and this request will be resubmitted this year.



## 6 • Recommendations and advice

- **Strong points :**

The strength of this unit lies in the opportunity that it will provide to the associated basic scientists and clinicians to combine mice and human models in order to better understand the consequences of pathological signaling in hematologic malignancies. These individuals have already performed extensive research together and the request to form this unit is the logical and consolidated next step of their interactions. The synergy between the clinicians and scientists has the potential to lead to critical new research and important discoveries in hematologic malignancies.

- **What needs to be improved :**

The visiting committee concluded that it will be important for the unit to recruit at least one additional senior scientist (i.e. INSERM/CNRS) in order to be able to achieve the goals that were set forth. There are presently only two full-time tenured scientists in the unit (one of whom is the director of the unit) and some of the experiments proposed require a high level of investment at a senior level. The visiting committee trusts that following the creation of this unit, the scientific ambitions of the associated scientists will blossom.

- **Recommendations :**

The visiting committee was highly supportive that this unit be created as a mixed INSERM/ university structure.

**Le Président**

Monsieur le Professeur AUBERT  
AERES  
20 rue Vivienne  
75002 Paris

Villetaneuse le, 29/05/2008  
Référence : DB/JLS/2200/N° 157

Monsieur le Professeur, Cher Collègue,

Parmi les projets évalués par l'AERES, dans la perspective de son prochain contrat quadriennal, notre université, a soumis un dossier de demande d'association à l'INSERM, dont le porteur est le Dr Nadine VARIN-BLANK, DR2 INSERM, sur le thème « Adaptateurs de signalisation en hématologie ».

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Ce projet associe un groupe de chercheurs de l'Institut Cochin et les biochimistes et hématologistes Hospitalo-Universitaires de l'EA 3406 de notre UFR médicale.

Je tiens à confirmer par la présente que je fais miens les propos qui ont été tenus, au nom de l'université, par mon prédécesseur, lors de la visite des experts de l'AERES le 4 février dernier et tout le prix que j'attache personnellement à sa réussite.

Ce projet est d'une très grande importance pour notre université. Il est, en effet, un élément capital dans notre politique de structuration et de développement de nos activités de recherche dans le domaine biomédical.

La note A qui lui a été attribuée par l'AERES conforte notre choix et valide la décision que nous avons déjà prise de le soutenir, en mettant à sa disposition 250 m<sup>2</sup> de locaux, dont l'aménagement est en cours et en prévoyant l'affectation d'emplois (ITA et / ou enseignants-chercheurs) en jouant sur les premières opportunités rendues possibles à l'occasion de redéploiements internes.

Veillez agréer, Monsieur le Professeur, et Cher collègue, l'expression de mes salutations distinguées.

Jean-Loup SALZMANN





Paris le 8/5/2008

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

### Response to the Report from the visiting committee

- 1. Short presentation of the research unit

Our unit has effectively 5 lab members having a HDR but two additional members have pending HDR that will be defended before fall.

We have also 10 additional manuscripts currently submitted.

- 2. Preparation and execution of the visit

The committee had the opportunity to visit our own facilities (cellular and tissue « tumorothèques », cytometry with two FACS Canto) and also several shared core facilities already on site such as the animal house and the proteomic laboratory. We are currently in the process of acquiring an additional cell sorter that will be available for some other teams located at the medical UFR of Bobigny.

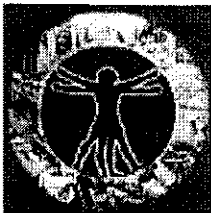
- 3. Overall appreciation of the activity

We want to point out that although the clinicians and university members are actually located within the nearby Hôpital Avicenne site they have no dedicated laboratory space within the University Paris 13 campus. Laboratory space and offices for all members of the unit will be available after completion of renovation at the University Paris 13 campus and actual laboratories will function as "transfer laboratories".

Renovation that will allow the fusion of the team is under process at University campus.

- 4. Specific appreciation team by team

Regarding the comments on the first group constituting the new unit, it is important to point out the change in the focus of their study toward the physiological relevance of their animal model in the context of the projects of the new unit. The ongoing projects are really focusing on understanding the role of the Vav and Lnk/APS families of adaptor proteins in B cell development and maturation with special emphasis on B1 lineage that represents the more proximal model to the pathologies studied. Since the team is aware of the competitive fields in which they are engaged, the members want to focus on projects where they are internationally recognized for their leadership. Support and synergy on these projects will be given by specialists present at the Paris 13 campus; such as characterization of transcriptional partners of Vav/STAT in normal and pathological B cells.



**Unité de Formation et de Recherche - Santé, Médecine, Biologie Humaine  
Léonard de Vinci**

The very fruitful exchanges between the clinically oriented group at Avicenne and the team 31 at Institut Cochin have resulted in co-authorship of several publications. They also share several grants they obtained together such as the Bioprize in oncology 2006 based on their collaborative work with the R and D Becton Dickinson USA. Finally this joined team has an ongoing patent request based on the project.

The director of the proposed unit is also aware of the need to recruit at least one additional full time INSERM or CNRS scientist. Regarding this comment, the future unit is presently presenting for the EPST recruitment one post-doctoral fellow who has joined the team last year after a very productive post-doc in Canada and who has a high training on these projects. Another post-doctoral fellow will also be proposed for recruitment as Ingenieur de Recherche at the University. Finally we want to remind the committee that our focused project fits within a “monoéquipe” type of project.

*[Handwritten signature]*

Nadine Varin-blank

**Le Président  
de l'Université Paris 13**

**Jean-Loup SALZMANN**

