NF-KAPPAB - Différenciation et cancer

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

NF-kappaB, Differentiation and Cancer

Under the supervision of the following institution:

Université Paris Descartes

February 2013

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 (and, when necessary, its in-house teams) received the following grades:

- Grading table of the unit: NF-kappa B, Differentiation and Cancer

C1	C2	C3	C4	C5	C6
A	A	A	A	B	A

Evaluation report

Unit name:	NF-kappa B, Differentiation and Cancer
Unit acronym:	
Label requested:	University E.A. with CNRS label
Present no.:	INSERM U 1016, CNRS UMR 8104, Institut Cochin
Name of Director (2012-2013):	Mr Pierre Olivier COURAUD
Name of Project Leader (2014-2018):	Ms Véronique BAUD, Mr Thierry MOLINA

Expert committee members

Chair:	Mr Jean-François PEYRON, INSERM, Centre médecine moléculaire, Nice
Experts:	Mr Salem CHOUAIB, INSERM, Institut Gustave Roussy, Villejuif, France
	Ms Urzsula HIBNER, CNRS, Montpellier (representative of the CoNRS)
	Mr Neil PERKINS, Newcastle University, UK

Scientific delegate representing the AERES:

Ms Sylvette TOURMENTE

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

Mr Stephano MARULLO, Université Paris Descartes

Mr Jean-Michel SCHERRMANN, Faculté de Pharmacie

Mr Yannick JACQUES, CNRS-INSB

1 • Introduction

History and geographical location of the unit:

Ms Véronique BAUD joined Institut Cochin in 2004 upon return from a post-doctoral period in San Diego USA. After 3 years as a member of a team, she obtained an independent status as team leader of a "Groupe Cochin" in October 2007. The team, which has recently associated with a group of clinicians, one of whom is a co-PI of the present project (Mr Thierry MOLINA) will now move to the Faculty of Pharmaceutical Sciences of the Paris 5 University to develop a project centered on the alternative pathway of NF-κB signalling in B lymphoid malignancies.

Management team:

During the period under evaluation (2007-2012) the team increased in size from 1 permanent scientist (VB), one technical support and 1 PhD student to 7 members in 2012 (2 permanent scientists, 2 clinicians, 1 permanent CNRS engineer, 1 post-doc and 1 PhD student). 2 PhD theses were defended (2007 and 2012) and 7 master students were trained in the lab (3-4 months rotations). One PhD thesis is ongoing (2011-).

Ms Véronique BAUD and Mr Thierry MOLINA are candidates for an EA research unit at University Paris Descartes and an ERL CNRS label.

AERES nomenclature:

SVE1-LS4

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	1 (40)	1 (40)	1
N2: Permanent researchers from Institutions and similar positions	2 (200)	3 (300)	2
N3: Other permanent staff (without research duties)	2 (130)	4 (170)	1
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)			
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	1 (100)	1 (100)	1
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**6**	**9**	**5**

Percentage of producers	***100 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit*	3	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	2	3

2 • Assessment of the unit

Strengths and opportunities:

(1) The area of research is very interesting. Although NF-kB has been studied for more than 25 years, the focus in recent years has been on the upstream signaling components, and in particular the processes leading to activation of the IKK complex in the 'classical' pathway. The study of the function of the subunits and RelB in particular of the non canonical NF-kB pathway, has consequently been neglected. In particular, the advent of many powerful new technologies has, in general, not been fully exploited to investigate the function of these proteins. Given our increasing understanding of the role of NF-kB in cancer, and a growing appreciation of the role of the 'alternative' NF-kB pathway, a consequence of this is that the work proposed by the Baud/Molina group is both timely and exciting. Specific strengths include:

- An exciting research program ;
- The solid previous track record of the two PIs ;
- Good visibility and contacts (national and international) ;
- Many collaborations (although this could also be a threat – see below) ;
- The capacity to ensure adequate funding through ANR BiotecS (2012-2015), INCa Lymphoma Network.

(2) The proposed projects are based on a significant amount of solid recent data, much of which has been published. The outlined programme of work is a good balance between follow up studies based on these data combined with further 'discovery' elements such as proteomics and transcriptomics.

(3) The involvement of Mr Thierry MOLINA will help the team translate their work from the laboratory to a clinical setting, which will increase the overall impact of their research.

Weaknesses and threats:

(1) It is unclear whether the new environment at the Faculté des Sciences Pharmaceutiques et Biologiques will be optimal for the group. Although there is potential for collaborations with established groups with expertise in the synthesis of pharmacological inhibitors or crystallography/NMR, no clear and concrete contacts have been established yet. Furthermore, while the team has established outside collaborations to analyze proteomics, transcriptomics and ChiP-Seq data, it is not clear if such expertise, in particular bioinformatics, exists at the new location of the group. Although these approaches can be outsourced to collaborators in the longer term it is often more efficient to be able to perform these on site.

(2) Five subprojects are planned with somewhat limited workpower: 1.5 to 3/4 full time equivalent each. There is therefore a recognized need for recruitment of additional research staff in a near future. Before this happens, it is difficult to imagine that all projects can be carried out at an internationally competitive level.

(3) It is not clear if one engineer from CNRS, already in the group since 2005, will be allowed, for administrative reasons, to follow the team.

(4) The level of international competition is high (446 references in the web of science for RelB in the last 10 years, 430 for NF-κB and leukemia or lymphoma, 100 for RelB leukemia/lymphoma).

Recommendations:

Given the size of the team, more focus is recommended with clear prioritization of the different projects.

To facilitate the completion of the ambitious research programme, the plan to recruit a young and highly motivated researcher for a permanent position should also be a priority.

Emphasis should be placed on ensuring good integration of the group with other researchers at the new campus.

Also, it is very important that this small team improves its attractiveness towards students. The projects would benefit a lot from the recruitment of more post-docs and PhD students.

The committee recommends caution about the team's involvement in too many projects that could be considered opportunistic as opposed to the well-focused research presented in the report. Although leading to co-authorship of many papers, outside collaborative projects may distract from the core efforts constituting the lab's main project.

3 • Detailed assessments

Assessment of scientific quality and outputs:

The group is internationaly recognized in the field of NF-kB and has published some highly original work establishing the concept of RelB as a tumor suppressor in p53 wt tumors (Oncogene, J. Biol. Chem.). The Oncogene paper in 2012 will likely be highly cited. The work will make a significant contribution to the field by shedding light on the alternative pathway of NFkB in B cell lymphoma development. The group has identified new regulatory components of the IKKa complex that may define an original signaling complex for DNA damage. Thus, although the overall output in terms of the number of publications from the team's own projects (i.e. outside of collaborations in which no team member is a senior author) is not very high, the work is of good to very good quality.

Assessment of the unit's academic reputation and appeal:

This is exemplified by invitations to speak at international conferences (VB: Keystone, 2 international workshops on NF-kB; TM: 2 European Hematology workshops). Moreover, there are established networks with industry (ANR) and clinics (NFkB and lymphoma). There is recognised expertise in NF-kB signalling. However, although the group has grown in size during the period of evaluation, its attractivness to students and young researchers is still insufficient.

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

The team has established industrial contracts with the clear potential for development of inhibitors of the pathway.

There is evidence for some cultural activity (1 meeting organization) but there is necessity to improve in this area in the future.

Assessment of the unit's organisation and life:

Due to the small size of the team there was no real need for development of the particular management skills associated with larger organisations and so the committee did not feel it was possible to score this section. However It was noted that although there is evidence of a good “esprit de corps“ among the research group, there are concerns about the day to day management of the team, such as an over-reliance on the technical expertise of one engineer, where in the longer term training of all lab members might be beneficial. The committee of experts recommends the PIs evaluate the best way to manage this group to maximise scientific output.

Assessment of the unit's involvement in training through research:

Despite only one HDR at the beginning of the project, four M2, one M1 students, two PhDs were trained.

There is limited participation in teaching activities.

The committee noted that there appears to be limited attractiveness for foreign students (1 italian Master 2 student).

Assessment of the five-year plan and strategy:

The project is based on solid and published results from the group, with intelligent and ambitious goals. If it succeeds it will make a significant contribution to the field of NF-kB research. The group shares good collaborations with several researchers in the field.

However, the committee had some concerns. Although several people have been recruited to the project, there was concern about the overall feasibility, as the group is pursuing too many questions with limited human resources. Therefore, there could be a gap between the level of scientific ambition and the feasibility of the project. In addition to the number of lab members, there is also a concern about the overall level of funding and resources available to the group, which will limit the scope of their research. It may be necessary for the group to focus on specific, key goals of the project (such as the novel function and members of the IKKa complex).

The committee did note that one high level young researcher is planned for recruitment (Inserm/CNRS) and agreed that this would strengthen the team.

There was also concern about the immediate environment. The committee did not succeed in getting sufficient information concerning the new scientific environment as well as clear details about lab space.

The committee appreciated the strong support by the Dean of the Faculty to get the team as a first step towards an UMR application in the next 4/5 years.

4 • Conduct of the visit

Visit dates:

Start: Tuesday, 19, February at 8:30

End: Tuesday, 19, February at 5:00 pm

Visit site(s):

Faculté de médecine

Institution:

Institut Cochin

Address (no. street town):

24, rue du Faubourg Saint Jacques, Paris

Conduct or programme of visit:

The visit had been carefully prepared and members of the committee liked the scientific quality of the oral presentation.

8h30 -9h00: Closed door session: committee and AERES Scientific advisor

9h00 -9h15: AERES representative: the role and procedures of AERES : presence of all the team's members

9h15-10h15: Director of the Unit: Presentation of past activities and future projects

10H15-11H00: Discussion with the representatives of the managing bodies

11H00-11H30: Coffee break

11h 30-12h15: meetings with personnel (without direction and managing bodies)

Discussions with engineers, technicians, administrative

Discussions with staff scientists

Discussions with students and post-docs

12h15-13h30: Lunch

13h30-17h:

- Discussion with head of the unit

- Private meeting of the visiting committee and AERES Scientific advisor

17h00: End of the visit

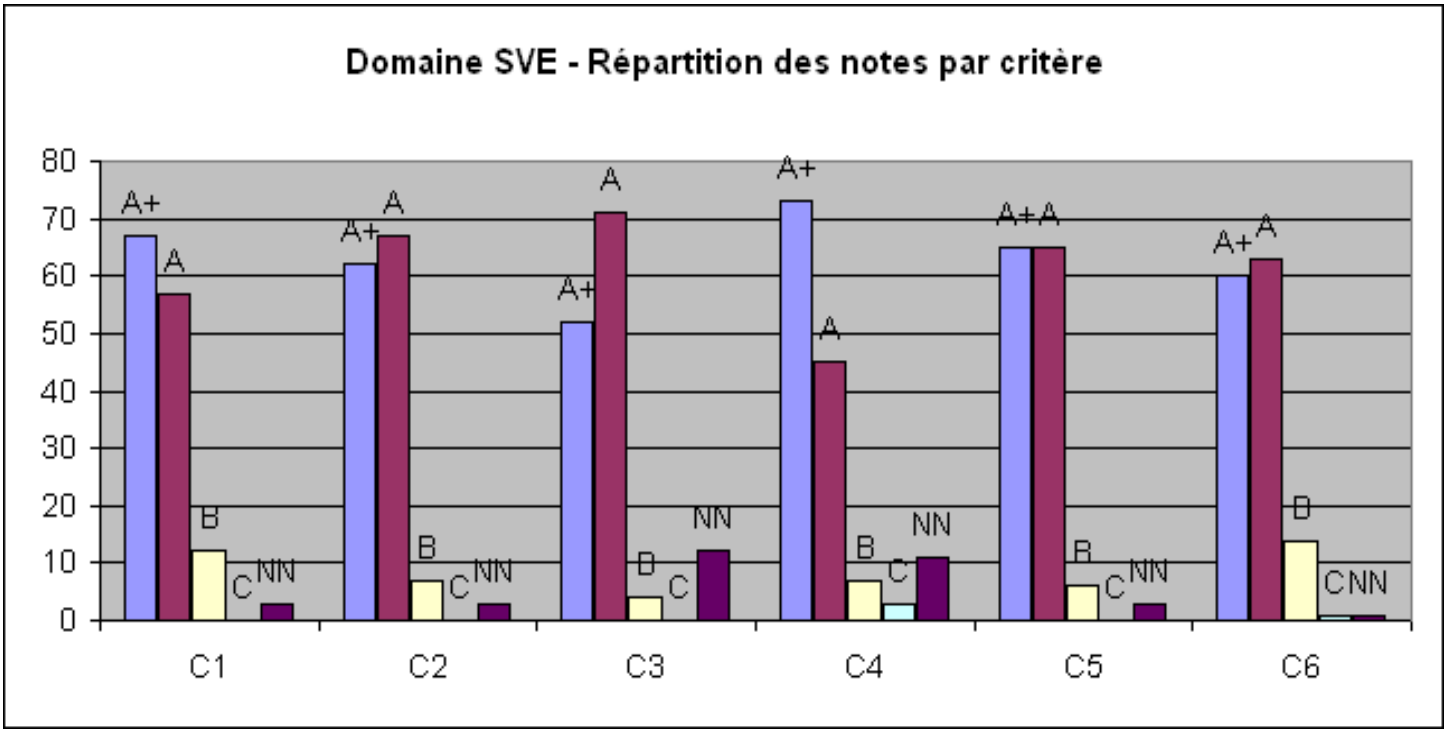
5 • Statistiques par domaine : SVE au 10/06/2013

Notes

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

Pourcentages

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%



6 • Supervising bodies' general comments

UNIVERSITÉ PARIS DESCARTES

Vice Président du Conseil Scientifique

Paris le 09.04.2013

Vos ref : S2PUR140006228 – NF-kappaB, Différentiation et Cancer - 0751721N

Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
Agence d'Evaluation de la Recherche et de l'Enseignement Supérieur
20, rue Vivienne
75002 PARIS

Monsieur le Directeur

Je vous adresse mes remerciements pour la qualité du rapport d'évaluation fourni à l'issue de la visite du comité d'expertise concernant l'unité « NF-kappaB, Différenciation et Cancer »

Vous trouverez ci-joint les réponses du Directeur de l'unité, Véronique BAUD, auxquelles le Président et moi-même n'avons aucune remarque particulière à apporter.

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

Le Vice Président du Conseil Scientifique

Stefano Marullo, DM, DesSci

Université Paris Descartes, Vice-présidence du conseil scientifique, 12 rue de l'école de médecine, 75170 PARIS cedex 06
Téléphone: 01 76 53 17 45; Courriel: stefano.marullo@parisdescartes.fr

Unit name: NF-κB, Differentiation and Cancer
Project Leader: Véronique Baud & Thierry Molina

Label requested: EA University Paris Descartes and ERL CNRS label

Director's comments on the Aeres report on unit "NF-kappaB, Differentiation and Cancer"

We thank the Aeres visiting committee for the fair assessment of our research unit and constructive remarks. Nonetheless, we would like to answer to the three main points highlighted by the committee:

1- Reasons for selecting the new host Institute

The visiting committee was eager to have some more information regarding our new environment at the Faculté des Sciences Pharmaceutiques et Biologiques.

First, we are pleased that the committee has appreciated the "*strong support by the Dean of the Faculty to get the team as a first step towards an UMR application in the next 4/5 years"*.

Second, we would like to reassure the visiting committee that by selecting the Faculté des Sciences Pharmaceutiques et Biologiques as part of the Université Paris Descartes, we will benefit out from an outstanding multidisciplinary working environment giving the opportunity to exchange idea with many scientists and benefit out of their expertise in various domains including novel anticancer therapeutics, signal transduction and biochemistry.

Third, it is important to note that since the visit of the Aeres committee on February, 19th, 2013, the Faculté des Sciences Pharmaceutiques et Biologiques was declared priority as part of the "plan campus" and was awarded a 50 M€ grant for its renovation, thus laying the foundations for a novel successful Research Center as part of the University Paris Descartes. Thus, there is no doubt that we will benefit out the required fully renovated lab space at the time of our arrival, and work in a very efficient and competitive environment.

Finally, regarding the core facilities, it is the political choice of the University Paris Descartes to have a network of core facilities located on different sites within Paris (e.g. Faculté des Sciences Pharmaceutiques et Biologiques, Institut Cochin, Necker). Thus, beyond the ones provided at the Faculté des Sciences Pharmaceutiques et Biologiques Pharmacie (e.g. animal facilities, cellular imaging, microscopy), we will get full access, when required, to the core facilities available at the Institut Cochin (located at walking distance), and at Necker (15 min by bus). It is particularly well

illustrated for bioinformatics (*"while the team has established outside collaborations to analyze proteomics, transcriptomics and ChIP-Seq data, it is not clear if such expertise, in particular bioinformatics, exists at the new location of the group"),* since we have already started to work in close contacts with Jean-Philippe Jais and Nicolas Cagnard at Necker for in-depth bioinformatics and biostatistics analysis.

2- Reinforcement of the team and prioritization of the different axis of the research project in regards to the size of the team

"To facilitate the completion of the ambitious research program, the plan to recruit a young and highly motivated researcher for a permanent position should be a priority"

We are aware that our team would benefit from reinforcement by young permanent position scientists. We are pleased that the committee highlighted that *"one high level young researcher is planned for recruitment and agreed that this would strengthen the team",* namely Emmanuel Derudder, a former PhD student in the group who is currently a post-doctoral fellow in Klaus Rajewsky lab (Max Delbrück Center for Molecular Medicine, Berlin, Germany) and would like to join us provided that he will be recruited by an EPST (CNRS-INSERM). He is an expert in Immunology and IKK/NF-κB conditional knockout mouse (Baud & Derudder, Curr Top Microbiol Immunol, 2011; Derudder et al., Nat Immunol, 2009; Sasaki, Calado, Derudder et al., PNAS, 2008; Sasaki, Derudder, et al., Immunity, 2006).

"it is not clear if one engineer from CNRS, already in the group since 2005, will be allowed, for administrative reasons, to follow the team"

Indeed, the transfer of Didier Bordereaux, our excellent CNRS senior research assistant (IE1), to our novel structure crucial might be a tricky issue. Nonetheless, he is deeply determined to keep working with us. Thus, we have good hope that, with the help of the CNRS i.e. the ERL CNRS label, we will keep working side by side for the years to come.

"Given the size of the team, more focus is recommended with clear prioritization of the different projects"

We agree with the committee and are fully aware that, in regards to the current size of our team, we have to focus on specific key goals of the project for an optimal development at an internationally competitive level. It is exactly the reason why, for the past months, we have given priority to the identification of new IKKα/RelB interacting partners and their functional characterization. It has led to three articles (JBC, 2011, Oncogene, 2012 + one article submitted), and still is the main topic of our ongoing research.

The committee recommends caution about the team's involvement in too many projects that could be considered opportunistic as opposed to the well-focused research project presented in the report. Although leading to co-authorship of many papers, outside collaborative projects may distract from the core efforts constituting the lab's main project

As experts in the field of IKK/NF-κB, we are often contacted to collaborate to scientific projects that required the evaluation of the IKK/NF-κB activation status. We would like to reassure the committee that we are cautious to only accept collaborations in regards to their scientific excellence and most complementary expertise. It is highlighted by top-level peer-reviewed collaborative publications (Nature Medicine, EMBO J, Blood,…).

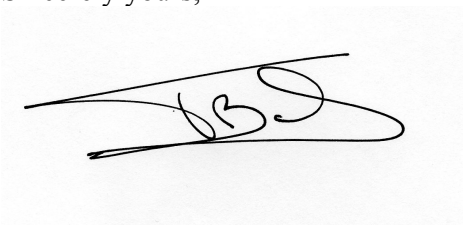
3- Improvement of attractiveness towards students

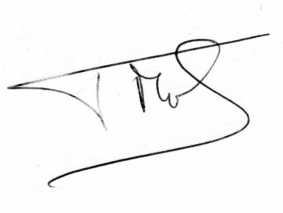
"The team will benefit out from the recruitment of more post-docs and PhD students"

First of all, we are pleased that the visiting committee pointed that despite only one HDR (V. Baud), *during the period of evaluation (2007-2012), five M2, one M1, two PhDs and 4 Post-Docs were trained.* The recent reinforcement of the team by two new members with permanent position and HDR (Thierry Molina & Corinne Besnard-Guerin) as well as our new very attractive scientific environment, will without a doubt allow us to recruit more Post-Docs and PhD students.

Finally, although *the committee noted that there appears to be limited attractiveness for foreign students* (*1 italian Master 2 student*), we would like to point out that during the period of evaluation we also have welcomed 1 Peruvian Master 2 student (Hugo Valencia) and 1 Albanian Master 2 student (Aleksandra Spiro).

Sincerely yours,





Véronique Baud

Thierry Molina