LD2 - Différenciation et progression tumorale des lymphocytes

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Lymphocyte differentiation and lymphoid disorders

LD²

Under the supervision of the following institutions and research bodies:

Université Paris 7 - Denis Diderot

Institut National de la Santé Et de la Recherche Médicale

Ecole Pratique des Hautes Etudes

January 2013

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

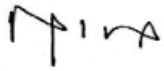
Research Units Department

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: Lymphocyte differentiation and lymphoid disorders

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

Evaluation report

Unit name:	Lymphocyte differentiation and lymphoid disorders
Unit acronym:	LD²
Label requested:	UMR_S, EPHE
Present no.:	EA3963
Name of Director (2012-2013):	Mr. Jean-Christophe BORIES
Name of Project Leader (2014-2018):	Mr. Jean-Christophe BORIES

Expert committee members

Chair:	Mr. Bertrand NADEL, University of Aix-Marseille, (INSERM representative)
Experts:	Mr. Eric JENKINSON, Birmingham, United Kingdom
	Mr. Philippe KASTNER, University of Strasbourg
	Mr. Jean-François MOREAU, University Bordeaux Segalen (CNU representative)
	Mr. Bernardo REINA SAN MARTIN, University of 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. Richard LAGANIER (Diderot University Paris 7)

Ms. Laurence LOMME (Inserm)

Ms. Jean Michel VERDIER (EPHE)

1 • Introduction

History and geographical location of the unit

The proposed LD^2 unit is a merge between three groups currently located and working in the IUH Hospital St Louis:

- Research Team EA3963 (University Diderot-Paris 7) directed by JC Bories (staff: ~17), which studies lymphocyte differentiation and lymphoid malignancy,

- A group (staff~5), currently integrated in the hematology department of UMR_S940, which studies epigenetic regulation of haematopoietic stem cell aging and B-cell differentiation,

- A group (staff~7), currently integrated in the UMR_S944, which studies the mechanisms controling early T-cell differentiation.

The merge is motivated by the complementarity of expertise of the three groups in the fields of B and T-cell differentiation and lymphoid malignancies, and aims to provide a valuable boost in translating science to the clinic.

Management team

The unit will be led by Mr Jean-Christophe BORIES, whose direction of the EA3963 unit currently encompasses a similar set of objectives. The new unit will be part of the IUH Paris 7, and benefit from its privileged association with hospital Saint-Louis. Relevant IUH infrastructure includes access to an animal house facility, Imaging/flow cytometry plateforms, a L3 laboratory (including a vectorology module), a genomic platform including stations for gene expression, CGH, sequencing (Miseq/Hiseq, illumina WGS).The unit will be composed of ~25 persons, and structured in 3 research themes:

- theme 1: "new pathways regulating B-cell developpement", led by JC Bories and comprising a- the study of ETS-1 target genes and b- the genetics of CVID,

- theme 2: "histone methyltransferase in B cell development and genomic instability", comprising a- the study of SUV39H1 and b- the MMSET,

- theme 3: "the role of TMEM131L in lymphoid development and function; functional screen of new regulators of early T-cell development in humanized mice".

All PIs have previous experience in team and unit management. Each team will be composed of 5-8 persons, some sharing their time in several themes. Weekly lab meetings with all staff (researchers and clinicians) are foreseen to allow group dynamics and articulation of know-how.

Management of the unit will be performed by the director, with collegial consultation of the PIs and staff for issues concerning life of the unit (safety, conception of research projects, ..). Funds allocated to the unit will be managed in a collegial fashion, while funds awarded to a specific member determined by this person.

Hygiene, safety, and ethical issues will follow legislation with oversight by a compliance officer.

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	6	6	6
N2: Permanent researchers from Institutions and similar positions	2	2	2
N3: Other permanent staff (without research duties)	6	6	4
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	1	1
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	10	9	9
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**25**	**24**	**22**

Percentage of producers	***100,00 %***

Nota: Counts "as at 30/06/2012" corresponds to the current EA3963 team added with members of the two groups that will join LD^2 team for the next term.

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	6	
Theses defended	8	
Postdoctoral students having spent at least 12 months in the unit*	6	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	7	6

2 • Assessment of the unit

Strengths and opportunities

The addition of 2 research teams (working on B-cell epigenetics and T-cell differentiation) to the former Bories unit develops a critical mass in cognate areas of research.

The unit has expertise in developing *in vitro* and *in vivo* models models to assess the impact of selected genes in lymphocyte development and cancer.

The unit has an excellent scientific output: 147 published articles, 32 with team members as senior authors, among which 6 with IF>10 (3 Blood, 1 J Exp Med, 2 N Engl J Med).

The unit has developped good national and international partnership in academia and clinics: coordination of the DefI group, coordination of the IFM ('Intergroupe Français du Myélome'). In addition they have industrial partnership on MM clinical programs (Celgene, AB science).

The clinical visibility in the fields of CVID and MM (national clinical referent) puts researchers of the Unit in a very favorable situation for transdisciplinary oriented research, in particular through exploiting defined cohorts of patients and large collections of patient's prospective/retrospective material.

The unit has shown ability to secure funding from various sources (100 k€/year) with 18% of this amount from the EPST and 22% from other various sources, and participated to the acquisition of large equipment (>600k€ with other labs).

It plays an active role in the teaching infrastructure of the Paris 7 University, and trains a high number of masters/PhD students.

Weaknesses and threats

The two added research teams with their new expertise will bring mutual added value if care is taken to foster strong collaborations across research topics. A clear strategy needs to be developped over the next period to ensure this.

Adding new topics that are not directly related to the pathologies strongly established in the associated/ongoing clinical programs brings a risk of dispersion, and will not help enhance the translational aim of the new Unit.

The unit must increase its resources to match the costs associated with research programs (especially in the genomics area).

Recommendations

The LD2 must carefully consider how to integrate the new themes in the unit, and precisely define how to reach common academic and translational objectives.

The committee recommends the Unit to increase scientific visibility by promoting the production of quality publications (IF >10) in all topics developed, with team members at strategic positions.

Expertise in bioinformatics should be re-inforced, either through collaboration or by hiring a bioinformatician, to allow for the best exploitation of the ChIP-Seq, RNA-Seq and exome sequencing data sets.

3 • Detailed assessments

Assessment of scientific quality and outputs

The unit studies the mechanisms of B and T lymphocyte development in humans and mice using both fundamental and translational research approaches with implications for cancer and immunodeficiencies. Based on a solid knowledge and expertise in the ETS family of transcription factors, they have generated ETS KO mice to better decipher its role in lymphoid development. They have shown that ETS deficient mice develop autoimmune diseases triggered by a deficit in T-reg cells, through epigenetic regulation of Foxp3 expression. They have also identified in ETS^{KO} mice a default of IgG2a secretion, and characterized that this was due to a default in T-bet expression via impaired STAT/ETS complex. Using a genetic screen in a large cohort of CVID patients, they have identified novel mutations in BTK, SAP, CD19, and in other genes suggesting polygenic causes, setting the rationale for genome-wide association studies. Using a large annotated series of MM patients with t(4;14) translocation associated with bad prognosis, they have identified FGFR3 and MMSET as potential therapeutic targets. They have evaluated the potency of kinase inhibitors on FGFR3 function in a preclinical xenograft mouse model, and initiated a phase III clinical trial. They also show in mice that HIV protease inhibitors can substitute proteasome inhibitors such as Bortezomib with reduced toxicity and induced drug resistance, and initiated a European phase III clinical trial.

The unit has made a number of important contributions in a highly competitive field with several papers in high quality journals (Blood, JEM, NEJM) and additional publications in mid-tier journals. The academic research work of the Director's group in particular is internationally very competitive, and it will be important for the whole Unit to achieve the same standard, while keeping the translational focus.

Assessment of the unit's academic reputation and appeal

The unit benefits from productive and promising national and international collaborations. Members of the unit are involved in coordinating national networks and have organized international meetings. The unit has attracted domestic as well as foreign Master students, graduate students, post-dcotoral fellows and permanent researchers.

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 new therapeutic tools for haematological disorders. This applied research will have direct consequences for socio-economic and health issues.

Large cohorts of patients (MM, CVID) have been created and exploited with clinical/economic partners. Team members are coordinators of two PHRC programs (Genetic screen of CVID; Nephropathy in Monoclonal Gammopathy) and one phase III trial (TK inhibitors in MM). The Unit has collaborations with Celgen (Lenalidomide in MM) and AB science (TK inhibitors in MM).

Assessment of the unit's organisation and life

The unit has established rules of governance and holds weekly scientific meetings and unit council every month where funding, administrative decisions, etc. are discussed in a collegial way. Funds awarded to the unit are distributed in a collegiate fashion; allocation of funds awarded to a specific member of the team is directed for use by that individual. The importance of scientific interaction between groups is recognised and encouraged by the Director.

Unit members are well versed in good lab practice and are conversant with ethical issues. A quality approach to scientific research activity of the unit has been formalised with the written rules of procedure.

Assessment of the unit's involvement in training through research

Several members of the unit teach in science and medical degrees (UFR Medicine Paris 7, Masters Santé & European Masters 2 genetics Univ. Paris 7). One of the team members set up and coordinates the DESC (Diplôme d'études specialisées) of "Immunology and Allergology" IDF, in which he and several other members perform teaching.

Four PhD students have graduated during the evaluation period.

The unit is involved in the training of multiple Master students, graduate students and post-doctoral fellows.

Assessment of the five-year plan and strategy

Much of the proposed work builds on existing strengths and activity and includes a number of novel and internationally competitive aspects. These will address key questions in lymphocyte development and control with potential translational impact in the understanding of disordered lymphocte function, including malignancy. In support of these goals a number of valuable experimental models, including functional genomic approaches applied in various in vitro and in vivo models have been established to determine the key role of defined signalling pathways and their underlying genetic control. These models are well established in the Director's group and likely to be highly productive. The dissemination of these approaches to other groups in the Unit will add particular value.

The team aims at dissecting the gene network controlled by Ets1 in developing B cells and B-cell leukemias, a logical step considering the success of the past research. Since they found that Ets1 is required for STAT5-dependent events (IL7-dependent proliferation, BCR-ABL induced transformation), they hypothesize that Ets1 and STAT5 synergize to regulate a set of common genes. The team will address this question with high throughput methods (ChIP-seq, microarrays). This is a cutting edge research proposal that will provide improtant insights into the role of Ets-1 and its target genes in the regulation of B-cell proliferation and the role of dyregulation in these pathways in B-cell malignancies. The proposed work is novel and has a high liklihood of success.

The genetic defects in CVID will be investigated. The team has the potential (cohort of patients and material) to perform it. The proposed work is well focussed, exploits expertise and techniques that are well developed in the unit and should provide important new information on the impact of these mutations on lymphocyte development and its control. The genome sequencing of the LOCID (late oneset ID) subgroup of CVID may help to focus the efforts in a new and original direction as the field is vast. It is likely to be important for translational medicine and patient's care. Large scale sequencing will certainly require more expertise in this technical field (bioinformatics) as well as increased funding.

The role of two Histone Methyltransferases (MMSET and Suv39H1) in genetic stability/instability in B-cell development and malignancy will be investigated. This is a highly topical area and, with the combination of expertise and techniques within the unit, it has a good prospect of success. t(4;14)-mediated deregulation of MMSET appears as a major factor in t(4;14)$^+$ MM pathogenesis, and the team aims at further dicephering the mechanistic causes involved. The proposed approaches are well-focused and should provide important insights on the role of MMSET in DNA damage response and MM pathogenesis. However, HMTs are usually targeting a large number of genes, and parallel genome-wide approaches such as ChIP-seq might be useful to elucidate the specific epigenetic landscape of MMSET deregulation in t(4;14)+ MM. The new epigenetic expertise added in the unit should bring an important added value to the swift development of this important topics and its translation to the clinics. The project also builds on previous results to further define the role of Suv39H1 and histone H3K9 trimethylation in B cell development, age-related decline in B lymphopoiesis and its impact in the onset of B cell mailgnancy. In particular, exploring the role of Suv39H1 in the response to programmed DNA damage induced by RAG1/2 and/or AID, through functional genomic approaches (including ChIP-Seq and translocation-Seq technology), should be informative and could provide a competitive advantage in a crowded field.

The team will investigate the role of TMEM131L in lymphoid development and the function of new regulators of early T cell development in humanized mice. The team has identified this new transmembrane protein that plays an important role at an early stage of human T cell differeniation. It has obtained evidence suggesting that signaling through this protein suppresses both the Notch and Wnt pathways. This discovery opens a new avenue of research as it raises several questions about upstream events and signaling mechanisms. However, it is still uncertain if TMEM131L exerts a conserved function across mammals or a human-specific function as it is expressed at only low levels in mouse thymocytes. A new mouse KO model generated by the team should clarify this question. The work is technically challening and in this regard of high risk, but potentially of high impact.

Overall, there is a good balance between fundamental and translational research. Most aspects of the proposed five-year strategy are based on solid grounds and have high likelihood of success; the Director is well-aware of the more risky components. The very high quality of collaborations should provide further competitive advantage.

4 • Conduct of the visit

Visit date:

Start: Thursday, January 31st 2013, at 8AM

End: Thursday, January 31st 2013, at 3PM

Visit site:

Institution: Institut Universitaire d'Hématologie, Hôpital Saint-Louis

Address: 1, Avenue Claude Vellefaux, Paris

Conduct or programme of visit:

Time: from 8:00 to 8:30

Door-closed meeting: Committee members and AERES representative

Time: from 8:30 to 8:45

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

Time: from 8:45 to 9:45

Presentation of theme 1:

'New pathways regulating B cell differentiation, genomic stability and B cell malignancy' (head: Mr Jean-Christophe BORIES)

Time: from 9:45 to 10:15

Presentation of theme 2:

'New pathways regulating T cell development in humans' (head: Mr Bruno CANQUE)

Time: from 10:15 to 10:45

Coffee break

Time: from 10:45 to 11:30

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

- PhD students and postdoctoral fellows
- engineers, technicians and administrative assistants (including technician CSS7)
- researchers with permanent position (except the unit's director and theme-leaders)

Time: from 11:30 to 12:00

Meeting with representatives of the University Paris VII, the Inserm, and the EPHE:

- *Prof. Richard LAGANIER, chairman of the Scientific Counsel, Paris Diderot University*
- *Ms. Laurence LOMME, ADR Inserm*
- *Mr Jean Michel VERDIER, EPHE*

Time: from 12:00 to 13:00

Lunch-buffet

Time: from 13:00 to 13:30

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

Time: from 13:30 to 15:00

Closed-door meeting of the committee and AERES representative.

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

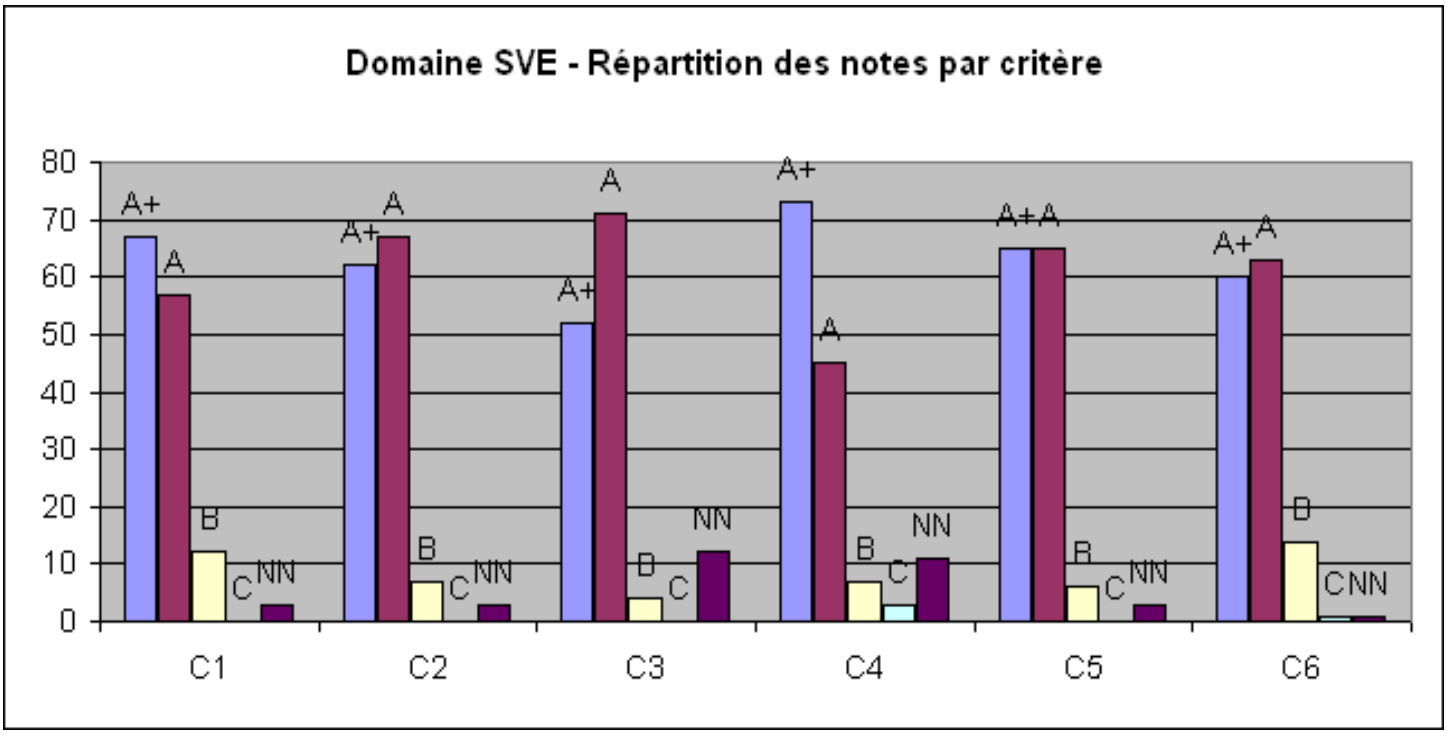
Grades

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 DIDEROT PARIS 7

Le Président

P/VB/LB/NC/YM – 2013 - 108
Paris, le 18 avril 2013

M. Pierre Glaudes
Directeur de la section des unités de l'AERES
20 rue Vivienne
75002 PARIS

S2PUR140006347 - Différenciation et progression tumorale des lymphocytes - 0751723R

Monsieur le Directeur,

Je remercie les membres du comité de visite de l'AERES pour la production du rapport très détaillé sur la situation du laboratoire « Lymphocyte differentiation and lymphoid disorders » et les remarques constructives formulées. Le directeur a élaboré dans sa réponse les éléments permettant de répondre aux recommandations du comité.

Je me réjouis des appréciations élogieuses qui sont portées sur ce laboratoire dont vous avez souligné l'excellente qualité des publications. Le rapprochement de plusieurs équipes a permis la mise en cohérence et en pratique de la complémentarité des axes de recherche et la transdisciplinarité attendue permettra d'accroitre encore la visibilité internationale déjà forte de cette unité.

Je note avec plaisir que l'implication importante des membres de l'unité dans les activités d'enseignement à Paris Diderot est considérée comme une force par le comité.

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

Vincent Berger

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SORBONNE PARIS CITÉ SUPÉRIEUR RECHERCHE ENSEIGNEMENT

Laboratoire– EA 3963 –Université Paris Diderot
« Différenciation des cellules B, hémopathies lymphoïdes et déficit de l'immunité humorale »
Directeur : Jean-Christophe BORIES

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Paris, le 5.04.2013

Monsieur le Président,

Nous avons pris connaissance du rapport du comité de visite de L'AERES qui a évalué notre projet d'unité de recherche "Lymphocyte différenciation and Lymphoid disorders" (LD^2) le 28/01/2013. Dans ce document, la présentation des groupes de recherche, leur localisation géographique et l'organisation choisie sont rapportées fidèlement. De même, le recensement des moyens humains impliqués dans la future unité, leur production scientifique et la description du projet de recherche sont rappelés d'une façon satisfaisante.

Le rapport souligne les nombreuses forces et opportunités de notre projet. En particulier, la réunion de plusieurs groupes, donnant naissance à une unité de taille significative tout en préservant l'unité thématique, est jugée très favorable. Le comité apprécie également la complémentarité de nos expertises scientifiques, la quantité et l'excellence de nos publications, la qualité et la diversité de nos partenariats qui nous donnent accès à de larges séries de patients, notre capacité de financement et, enfin, notre implication dans l'enseignement.

Cependant, afin d'augmenter nos chances de succès, le comité nous adresse trois recommandations.

1) Tout en insistant sur la plus value que représente le rapprochement de plusieurs groupes de recherche, le rapport recommande de veiller au risque de dispersion thématique inhérent à cette situation.

2) Afin que, dans son ensemble, notre unité puisse gagner en lisibilité, le comité nous incite à ne pas limiter la parution de publications à haut facteur d'impact (>10) à certains thèmes de recherche, mais d'appliquer cette politique éditoriale à tous les axes du projet.

3) Le rapport recommande de renforcer les moyens humains attribués aux analyses bioinformatiques nécessaires à la réalisation du projet.

Nous partageons cette analyse et souhaitons exposer la façon dont nous allons suivre ces recommandations.

1) Notre demande de création d'unité "mono-équipe" atteste de notre volonté d'intégration des différents groupes de recherche. Afin de concrétiser et de pérenniser la convergence thèmatique, les membres de l'unité ont déposé ensemble (et déposent encore) des demandes de financement (équipe LNCC 2012, Programme labellisé Fondation ARC 2013 et Programme Urgences de la recherche FRM 2013) qui augmenteront les moyens attribués à notre projet commun. En exerçant une certaine pression financière, cette stratégie favorisera la réalisation des objectifs académiques et translationnels identifiés dans le projet.

2) Nous souhaitons évidemment que les résultats de chaque thème de recherche soient publiés dans les meilleures revues. Comme l'a souligné le rapport, la création de notre unité permettra d'associer des expertises complémentaires autour d'un projet commun. De plus, nous avons mis en place des collaborations avec des laboratoires d'excellence qui rendront nos projets plus compétitifs. Cette organisation permettra d'élever le niveau de technicité consacré à chaque thème de recherche, d'accélérer l'avancée des travaux et, ainsi, d'assurer une lisibilité plus homogène des publications de notre équipe.

3) Nous avons choisi une stratégie à trois niveaux pour accéder à une expertise bio-informatique performante.

- Des collaborations externes avec des laboratoires à l'expertise reconnue (Prs JL Casanova, F. Alt, R. Hendricks et DR. Higgs) ont été établies.

- Des collaborations internes avec la plateforme de bio-informatique de l'IUH (deux bio-informaticiens à temps plein) et la société *GenoSplice*, située dans nos locaux et avec laquelle l'IUH a développé un partenariat pour l'analyse des données de séquençage, sont déjà fonctionnelles.

- Le recrutement de personnels formés. Pour cela nous avons recruté des chercheurs sur des contrats de recherche (ARC pour le Dr Garrick et FdF pour le Dr Nguyen) qui se présenteront prochainement aux concours de chargé de recherche.

Cette organisation nous assure dès aujourd'hui l'accès à une expertise bio-informatique de haut niveau que nous souhaitons pérenniser grâce au recrutement de chercheurs.

Nous nous réjouissons des conclusions positives du comité de visite et nous espérons que la mise en œuvre des recommandations du rapport favorisera la réalisation de notre projet.

Jean-Christophe Bories.

"L'EPHE tient à remercier les membres du comité de visite pour la qualité de leur rapport concernant le laboratoire « Lymphocyte differentiation and lymphoid disorders » (LD2). Elle note l'appréciation très positive concernant le regroupement des différentes équipes, la haute tenue des publications de l'unité, ainsi que le bon équilibre entre recherche fondamentale et recherche translationnelle.

Elle n'a pas de correction à formuler au titre des « erreurs factuelles ».

Au titre des « observations d'ordre général », l'EPHE observe que le projet proposé par son équipe est qualifié de "technically challenging" et à haut potentiel et qu'il ouvre de nouvelles voies en recherche, ce dont elle se réjouit. Elle regrette toutefois que le comité n'ait pas fait mention de l'implication des enseignants-chercheurs de l'ephe dans l'enseignement (p.7)."

Denis Pelletier
Président de l'EPHE