EDC - Epigénétique et destin cellulaire

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Epigenetics and Cell fate

Under the supervision of the following institutions and research bodies:

Centre National de la Recherche Scientifique

Université Paris 7 - Denis Diderot

January 2013

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

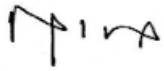
Research Units Department

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: Epigenetics and Cell fate

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

Evaluation report

Unit name:	Epigenetic and Cell fate
Unit acronym:	
Label requested:	UMR 7216
Present no.:	
Name of Director (2012-2013):	Mr Jonathan WEITZMAN (Director) Ms Valérie MEZGER (Deputy Director)
Name of Project Leader (2014-2018):	Mr Jonathan WEITZMAN (Director; Prof. University Paris Diderot) Ms Valérie MEZGER (Deputy Director)

Expert committee members

Chair:	Ms Françoise DANTZER (IREBS, Strasbourg)
Experts:	Mr Joel DREVET (Laboratoire Génétique, Reproduction et Développement, Clermont-Ferrand) representative of CNU Mr Brian HENDRICH (Stem Cell Institute, Cambridge, UK) Mr Arne KLUNGLAND (Oslo University Hospital, Sweden) Mr Andreas LADURNER (Faculty of Medecine, Munich, Germany) Ms Chantal VAURY (Laboratoire Génétique, Reproduction et Développement, Clermont-Ferrand) representative of CoNRS Mr Jorn WALTER (Blueprint epigenome, Saarland,Germany)

Scientific delegate representing the AERES:

Mr Jacques HAIECH

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

Mr Marc BENEDETTI (University Paris - Denis Diderot)

Mr Thierry GRANGE (CNRS)

1 • Introduction

History and geographical location of the unit

The UMR7216 "Epigenetics and Cell Fate" was created in January 2009 by the Université Paris Diderot and the National Research Agency CNRS. The Laboratory is located in the campus Paris-Rive-Gauche (PRG) that houses additional entities in two adjacent buildings : The Institut Jacques Monod (IJM, UMR7592), the unit "Biologie Fonctionnelle et Adaptative (BFA, EAC 4413) and the Unit "Molécules Thérapeutiques in silico" (INSERM UMR-S 973). This location favors scientific collaborations but also provides the laboratory with the qualified technical facilities required for the efficient development of their research.

In the last AERES evaluation in 2008, the Unit was evaluated as a structure composed of 6 research teams led by highly qualified team leaders that formed the initial core of the new unit. During the last period, the 7 groups and the management worked hardly to (i) install the laboratory in a well-equiped shared space located in the 4th floor of the Lamarck building (ii) to develop several technology platforms (iii) and to built a coherent scientific project centered on Epigenetics and Cell Fate. In 2012 they recruited an additional young qualified female investigator that is building her own group. For the present AERES evaluation they decided to present the Unit in terms of two central themes: (i) Epigenetics, pluripotency and cell differentiation; (ii) Physiological impacts of epigenetics mechanisms in development and disease.

Management team

The management, administration and external representation of the UMR are assumed by a Deputy Director . The current Director and Deputy Director have been elected to continue their mission for the 5 years to come.

An Executive Board with the two directors and the group leaders meets on a regular basis and through a retreat and makes decisions on all aspects of the scientific and strategic policies, the management and the administration. A Laboratory Council (Conseil de Laboratoire) brings together the direction and a body of representatives of all the personnels. This Council meets approximately once a month to discuss on the organisation and life of the Unit, debate on funding issues, careers etc. A General Assembly of all members is organized once a year.

The UMR is served by a centralized secretariat composed of two persons that fulfill the role of Secretary and General manager .

AERES nomenclature

SVE1_LS2 Genetics, genomics, bioinformatics

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	7	7	7
N2: Permanent researchers from Institutions and similar positions	8	8	8
N3: Other permanent staff (without research duties)	10	10	7
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)			
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	8	5	5
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	33	30	27

Percentage of producers	***100 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	11	
Theses defended	12	
Postdoctoral students having spent at least 12 months in the unit*	8	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	8	9

2 • Assessment of the unit

Strengths and opportunities

In 2009, the Director and his unit (7 teams) had a piece of work in hand with a strong will to build a coherent and integrated set of interdisciplinary research projects centered around epigenetics and cell fate. The committee unanimously agrees that credit has to be given to the management, the goup leaders and the lab members for a successful organization created in a relatively short-period of time. The task was certainly not easy. In the last period, this unit has shown a very good potential to grow a coherent, well-equiped, young and dynamic unit structured around 8 teams as demonstrated by the following elements :

The unit has been able to attract highly qualified young researchers, particularly good and ambitious female investigators

The different groups develop complementary research projects and show a sustained commitment to (i) integrate their different strengths and expertise, (ii) to stimulate cross-feeding ideas, (iii) and to favor inter-team scientific collaborations with the common objective to organize their research in two major themes. If on the one hand this organization creates synergistic scientific opportunities, on the other it might be difficult for the management to clearly evaluate the feasability and to identify weaknesses such as it was the case for the visiting committee. Overall the appreciation of the science of this Unit is very good and robust, but there is place for improvement for specific projects/groups that should focus their efforts on well-identified priorities as suggested in the theme-by-theme analysis.

The significant number of invited lectures and the coordinations of collaborative studies are relevant indicators of the good reputation of the Laboratory. Nearly all groups are engaged in national collaborations and/or networks and some of them are involved in pivotal international collaborations/networks. We can recognize an important effort to participate or chair these network, which helps to place this unit in a competitive international position relative to other local units with interests in epigenetics.

An important effort of the Unit has also been placed in the development of novel technologies and bio-resources in addition to well-equiped technical platforms by combining the expertise and interests of the different project leaders. The laboratory received good support from the University for the recruitment of technical staff.

The committee was pleased to note that the Director, Deputy Director and group leaders were unanimously appreciated by the lab members. It appeared evident that the members are very pleased with the synergistic atmosphere and collaborations within the unit.

Weaknesses and threats

The committee recognizes the overall good scientific production since the unit has been created. However, if some projects/teams are remarkable because they are based on breakthrough achievements, have a proven potential to attract competitive external fundings and are developed by internationally-recognized project leaders, others appear less successful. These projects/teams would benefit from collegial help to get more efficient. Some of the projects/teams are too ambitious relative to the previous achievements and need refining (in the objectives) to focus the energies involved in the core-strengths of the group.

The committee noticed the absence of critical mass (especially PhD students and post-docs) in some teams or on some projects. This is particularly right for the team working on stress and brain development and the team working on RPTPs and neurodevelopment. These teams should be encouraged to recruit PhD students.

Recommendations

Considering the high number of projects per team and the shared motivation to create an integrated productive research organized around two themes, the unit is encouraged to plan an annual internal review/retreat for all the group leaders, which would allow them to critically evaluate the development of each objective and to identify and discuss on the more competitive and innovative projects, using each other as the most critical and supportive peers. The help of external reviewers should also be considered.

The committee encourages the Unit to continue their efforts to integrate in large international funding networks, thereby creating broader visibility as a unit and in the field.

The permanent scientific staff is encouraged to defend their habilitation (HDR) to facilitate the recruitment of PhD student and thereby increase the critical mass within some groups.

The committee considers essential to increase strength in bioinformatics and data analysis, possibly by recruiting an engineer, group leader or senior scientist with an expertise in bioinformatics.

The committee strongly advises the campus and the institutions to provide more lab space to the Unit. This would appear to be crucial for their development in order to reach critical mass and maximize synergies, thus further improving the quality of their research.

The administrative burden for the scientifically highly active director and co-director is relatively high. The committee supports the planned recruitment of a secretary in the coming years to replace a forthcoming retirement and the creation of a lab manager for the hESC culture, which could also provide technical support to one of the teams.

3 • Detailed assessments

Assessment of scientific quality and outputs

The initial challenge of this unit created in 2009 was to coordinate the interests of 7 different teams around a coherent scientific program organized in two themes. The committee unanimously recognized that this challenge has been fruitful placing the unit as pionneer in the creation of thematic-organized laboratories. The overal research activity has shown very good general progression in this short-time period generating quite robust science and placing this unit in good position for the coming years relative to other local institutes with interests in epigenetics.

In the last period (2007-2012), the unit has published 51 research papers (23 as first or last author + 28 as collaborative papers) and 28 review articles. They also have 14 submitted papers (10 as first/last author + 4 collaborative papers) indicating that 2013 will likely be a productive year. However there are some heterogeneity in the average number and quality of publications between the projects/themes. Whereas some projects generated several outstanding publications in highly-ranked scientific journals (Nature, Science, EMBO J., Blood, Oncogene, PNAS, Mol Cell, Hum. Mol. Genetics, NAR, Cancer Res J. Neuroscience, PLOS Pathogens, J Mol Biol), for others (i.e. brain development, RPTP and HSF) the publication record is slightly below what could be expected (1 Biol. Psychiatry, 1 J Cell Sci, 1 Infect Immun, 1 Antioxid Redox Signal, 1 Mol Biol Cell, 1 JBC). According to this statement, some scientific focus might at once become critical and is recommended.

Overall the unit has several important grants which make this unit well financed. Grants were obtained by applications to both national and international calls (including 7 ANR and 3 EC grants). The director of the Unit chairs a Laboratoire d'Excellence (Labex Consortium "Who Am I ?") and the laboratory also received important support from the University and the CNRS to build their structure.

Nearly all group leaders participate or chair scientific national and international networks (LIA, GDR, EC-funded network, DHU PROTECT etc..) that give them a very good potential in the highly competitive field of epigenetics, and sustain fruitful collaborations that generally lead to publications with very high impact.

Several lab members obtained prizes and awards, including an ERC award.

Assessment of the unit's academic reputation and appeal

The unit constitutes a unique interdisciplinary setting in a well-equipped infrastructure with very good/excellent connections to other supporting research institutions such as *Institut Jacques Monod, Institut Pasteur, Institut Curie, Hôpital Necker* and others.

The notoriety of the unit is indicated by the high number of invited lectures (over 150) given by the lab members over the last 3 years, their participation in the organisation of international scientific meetings and their involvement in large national and international networks (including DHU PROTECT, ERC starting grant, Labex, LIA Epigeno-stem, EC-funded framework Epigenesys). The Unit did attract two qualified young investigators, a brilliant female investigator enthusiastic to build her own promising team and a talented young scientist who has been awarded a Marie Curie International Research Reintegration Grant to develop novel plans in a well-established group. The Unit has also a good potential to attract doctoral and post-doctoral fellows that represent approximately 23% and 16% of the work force of the laboratory respectively; a significant number of them come from abroad.

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

This Unit has shown very good interaction with the cultural and social environment. Several lab members (3 project leaders) gave 13 public debates and wrote 9 articles in popular journals. As mentionned above, several lab members are also involved in various scientific boards (Editorial boards, Scientific and Administrative Councils).

Translational research has not been the priority of the Unit despite the obvious potential of epigenetic in clinical and pharmacological applications. During the last period the unit made the sensible choice to focus the research activities on fundamental questions to hold up the biology of epigenetic phenomena. The next period will certainly generate opportunities for economic valorization that the project leaders are encouraged to consider.

Assessment of the unit's organisation and life

Credit should be given to the management, the team leaders and the lab members for a pretty dynamic, interactive and healthy unit organization which was conducted in 3 years. This is exemplified by the creation of a Conseil de Laboratoire meeting once a month, the organisation of an annual Asemblée générale, weekly seminar sseries, the invitation of external national and international speakers on a regular basis (over 70 speakers invited during the last period), the organisation of an UMR retreat as well as a team-leader retreat to discuss strategic points. The Direction also produces a weekly electronic Newsletter well appreciated by the lab members.

Furthermore, during this period, the unit was able to catalyze good inter-team technical collaborations and to build a rich technical environment. The Unit has placed significant efforts in the developement of in-house technical facilities made available to researchers of the PRG campus : a platform for the production of lentiviral and retroviral vectors, a platform with expertise in epigenomic related technics, a platform for the cultivation of hESC cells and an imaging platform. The two first platforms are strengthened by the recruitment of dedicated engineers.

Assessment of the unit's involvement in training through research

The committee recognized a significant participation of nearly all members of the unit in teaching activities both in local Master degrees and in the PhD programs as well as abroad. Several lab members also chair or participate in the organization of a teaching module.

The overall implication of the Unit in training is very good : PhD students and post-docs represent approximately 40% of the laboratory members. However, the committee noticed some heterogeneity among the different groups/projects that should be improved. The recruitment of PhD students and/or post-docs on the projects focusing on (i) HSF in brain development and (ii) signaling pathways in brain development is encouraged to increase the workforce and improve the output.

Assessment of the five-year plan and strategy

Continuing and expanding on the major two themes as detailed in the theme-by-theme analysis. The overall plans represent solid and achievable goals for most of the main objectives. Globally the projects are scientifically sound and timely, but for some of them particularly in theme 2 there is an apparent discrepancy between the proposed objectives and the current taskforce, the potential to attract fundings or the preliminary achievements. It is therefore difficult to determine how sucessful they will be. A particular attention should be paid to critically evaluate these projects and prioritize if necessary for the years to come. The creation of an Scientific Advisory Board (SAB) including external experts of the overall developed research will certainly help.

4-b • Theme-by-theme analysis

Theme 1: Epigenetic Mechanisms

Manager's name: Jonathan WEITZMAN

Workforce

Theme workforce in Full Time Equivalents	As at 30/06/2012	As at 01/01/2014
FTE for permanent professors	1,5	1,5
FTE for permanent EPST or EPIC researchers	3,55	3,55
FTE of other permanent staff without research duties (IR, IE, PRAG, etc.)	4,8	5,3
FTE for other professors (PREM, ECC, etc.)		
FTE for postdoctoral students having spent at least 12 months in the unit	7	
FTE for other EPST or EPIC researchers (DREM, etc.) excluding postdoctoral students		
FTE for other contractual staff without research duties		
FTE for doctoral students	4,5	
TOTAL	21,35	10,35

• Detailed assessments

• The thematic area 1 for the UMR is divided into three biological focus areas:

Non-coding RNAs

Non coding RNAs (ncRNAs) are emerging as new actors in most aspects of gene expression. Several teams of UMR 7216 have studied ncRNAs implicated in the specification of higher-order chromatin structure. Two major themes related to the analysis of ncRNAs have been developed over the last three years: (1) Taking X-chromosome inactivation as a paradigm, ncRNA function and regulation in stem cell identity and fate have been studied; (2) The contribution of long ncRNAs in cell cycle and muscle differentiation has been explored.

Teams involved in ncRNA study have good to excellent potential as revealed by their results, success in grants and collaborations. It must be emphasize that results obtained on X-inactivation in both mice and human ES cells are remarkable and published in highly-ranked journals (Nature, Science, Hum. Mol Genetics, Mol Cell).

Projects for the years to come are ambitious. They aim at understanding the role of ncRNAs in the maintenance of pluripotency and cell fate decision upon differentiation cues. They will be also focused on the transcriptional diversity generated by RNA splicing. From the precedent years, teams have accumulated data and tools which totally justify the projects proposed.

Although in a highly competitive field of research, it can be anticipated that teams involved in these projects have the potential to succeed very well. They have their own niche on some aspects and have developed collaborations with others. The whole project is strengthened by the existence of cutting-edge projects carried out by outstanding researchers.

• Methylation mechanisms:

The role of methylation and demethylation of DNA and histones has attracted massive scientific attention in the last decade. The reversible nature of these modifications provides a basis for the understanding of the dynamic nature of mammalian gene regulation and their role in regulating homeostasis in the human system. During the last few years, the research unit "Epigénétique et Destin cellulaire" has published papers in two main areas of methylation mechanisms; the role of proteins that bind methylated DNA and the role of histone lysine methylation. For most studies, these phenomena are being studied on the subject of pluripotency and differentiation.

The unit has regularly published their work in well reputed international journals (including Oncogene, JBC, NAR, PNAS, Plos One, Cancer Res.). Moreover, they have contributed to, and co-authored, some very exciting collaborative studies (Science, Nature, EMBO J, Nature Struct. Mol Biol.). Altogether, the unit has a good to excellent track record in this subject.

While it should be evaluated how much effort the young and relatively small research groups can contribute in collaborative studies, it is impressive to see that they have expertise and time to contribute to collaborations outside the unit. Also, as the Centre as a whole is relatively small in size, external collaborators are crucial for most projects coordinated by the unit.

In conclusion, the unit certainly has a solid basis for future work on methylation mechanisms and it is nice to see that they propose to use current knowledge for more in-depth studies on the relevance for human disease. Such studies are also crucial for the Centre as a whole. Ideally, the different groups contributing to this topic should obtain more funding. With the work force currently available it is the committee's view that the projects concerning methylation mechanisms need to be more focused.

• Stress and the epigenome:

The theme of stress and the epigenome is receiving an ever increasing amount of attention, as it relates the impact also of environmental changes on human health. The overall theme is timely and bears significant scope for further research that can take advantage of novel imaging and functional genomics tools.

Teams involved in this area have good to excellent track record(PNAS, Oncogene, Nature, Science..), and have been measurably successful in obtaining outside grants and being engaged in local and international collaborations. The recruitment of one new group leader in the area of DNA damage is a very good complementation of the UMR's activities in this area. The theme would appear to be ideally suited to allow the UMR to develop an 'environment-centered' profile that is highly complementary to the more basic, fundamental epigenetics activities at the Institut Curie, for example.

The future goals are broad and ambitious at the same time. The site visit was useful, as the written report gave an even broader picture of what may actually be intended or planned going forward. Indeed, the committee's advice would rather be to focus all activities within the theme and within each team on a select number of stress signals and stress sensors, and not necessarily to try to seek a comprehensive answer or general footprint for stress signaling.

The focus should be on those stresses that can be fully addressed experimentally and in a timely fashion using in-house resources and/or local collaborations. The research portfolio of the UMR in this area should be focused on those activities that allow the wider epigenetics community to immediately identify the research with the UMR and the particular PI in question. The integration of DNA damage and repair pathways in this context is strongly supported. The topics of stress responses in cell fate decisions and upon *Theileria* infection also complement the overall theme well. Both for junior and established groups, the focus needs to be on developing a limited set of high potential and high interest projects that maximize the groups's and the unit's core expertise.

Considering the research theme's wide appeal to the general and scientifically interested public, the Unit may also do well to continue to develop these research activities as a platform for outreach, dissemination and teaching activities.

Conclusion

• Overall opinion of the theme:

The unit has produced numerous high-quality publications on the theme and collaborated on some outstanding studies. Furthermore, this theme will benefit from the recent recruitement of a female young investigator developing interests in Epigenome integrity in response to DNA damage. It has all the potential to become an internationally visible thematic area for the unit.

• Strengths and opportunities:

Altogether the unit has expertise on all relevant areas for basic research on mechanisms related to methylation marks on DNA and histones. Altogether, the teams involved have substantially contributed to a better understanding of epigenetic mechanisms including the role of non coding RNAs, methylation mechanisms and the consequences of stress conditions on the epigenome. From the precedent years, they have accumulated data and tools which totally justify the projects proposed and offer the potential to succeed very well. The opportunity to take this knowledge into more clinical relevant studies was presented and should be pursued. The teams involved are expected to continue successfully grant acquisition, education of young scientists and local and international collaborations. New recruits underpin the theme's evolving strength.

• Weaknesses and threats:

Some of the individual groups on the theme have a sub-optimal critical size and need to attract more funding. Some of these smaller teams would benefit from focusing on a more defined, less broad and thus clearer research direction, since the resources are limited and therefore projects cannot by as multidirectional as they were presented.

• Recommendations:

The possibility to attract a new group focusing on more biochemical methods related to methylation marks can be considered- to broaden the research tools on methylation and to compensate for the current lack of funding for other groups.

Theme 2: Physiopathology in development and disease

Manager's name: Valérie MEZGER

Workforce

Theme workforce in Full Time Equivalents	As at 30/06/2012	As at 01/01/2014
FTE for permanent professors	2	2
FTE for permanent EPST or EPIC researchers	3,2	3,2
FTE of other permanent staff without research duties (IR, IE, PRAG, etc.)	4,2	4,7
FTE for other professors (PREM, ECC, etc.)		
FTE for postdoctoral students having spent at least 12 months in the unit	2	
FTE for other EPST or EPIC researchers (DREM, etc.) excluding postdoctoral students		
FTE for other contractual staff without research duties		
FTE for doctoral students	7,5	
TOTAL	18,9	9,9

• Detailed assessments

The major aim of Theme II is to gain novel insights into pathophysiological mechanisms controlling cellular differentiation and cellular memory in complex disorders such as Schizophrenia (SZ), Autism (ASD), ICF Syndrome and cancer. Most projects are based on work performed on epigenetic mechanisms analyzed in Theme I. The main contributions of Theme II to the past funding period (2009-2012) came from the groups of P.A. Defossez, C. Francastel, V. Mezger, J. Sap and J. Weizmann. The proposed program for the period 2013-2018 will also include contributions by the groups of C. Rougeulle and S. Ait-Si-Ali. During the 2009-2012 reviewed period, there was a great disparity in the publication output and funding levels of the different teams.

The UMR has initiated promising work with respect to the experimental aims of Theme II. The proposed program requires strong interactive and collaborative efforts of the unit, however the report leaves it rather vague as to "who is doing and contributing what." Moreover the proposed work program is only partially supported by publications or detailed documentation of unpublished results. It is therefore sometimes difficult to evaluate the potential of some of the proposed projects. While the general scientific goals of Theme II are of strong general scientific interest, some projects appear to be built on rather speculative ground. The project presentations - both in the form of talks and poster presentations - provided a better insight into the molecular background of the proposed projects. It became apparent that groups indeed initiated interactions over the past funding period as a basis for the proposed projects. This interaction will be continued and intensified in stronger collaborations combining different expertise and by collaborating with outside partners particularly with respect to studies on human cells.

The great and common spirit of the unit to achieve the ambitious goals is clearly recognizable – however strategies for joint comprehensive studies (screenings, interactions, knockouts and knockdowns) could be more clearly defined. The added value of the interactive structure of the unit should be emphasized in the next report.

One specific research project is rather out of focus within the general theme of the unit. The main objective of this research project is to explore the phosphatome in order to apprehend genes that could be relevant for neural differentiation and psychiatric diseases. The projects proposed in part "*a*" include a follow-up on the role of RPTP¤ and PTPRz in the control of oligodendrocyte lineage, and a search for other PTPs in the same lineage that may antagonize the RPTP actions. This exhaustive approach might not be the most judicious. As they have what looks like an SZ phenotype in their *Ptpr*$^{-/-}$ mice it might be more efficient to analyze more in depth that particular model and as it is proposed to put their forces in the analysis of how RPTP¤¤controls radial neuronal migration and NMDA-receptor function. The last project in which lentiviral knockdown in primary neuronal cultures is envisaged to identify phosphatases that affect neuronal differentiation is hampered by the high number of phosphatase genes identified in their original screen and the unavailability of the L3 facility for the time being. Although the biochemical expertise of the group leader is valuable for the rest of the unit it is less clear whether this research will benefit to the core project developed by the other teams.

An other program of Theme II for 2013-2018 focuses on neurodevelopmental disorders organized in five different work packages. Though not explicitly mentioned several groups are apparently contributing to individual work packages. The topics cover aspects of brain development (oligodendrocyte formation and differentiation), neuropathologies such as schizophrenia and fetal alcohol syndrome and the cellular response to stress. The research will mainly use mouse (knockout) models as research objects complemented by few studies using primary human material (e.g. OMSCs). In particular they will study the role of PTPR mediated cell signaling, the transcriptional control by HSFs and the role of DNA- and histone-modifiers/readers (ZBTBs, DNMT3B). The lack of experimental detail in the presentation of many of these projects left the reviewers unable to properly assess the feasibility or justification of much of this work.

An other focus in this theme mainly concerns the functions of the different proteins being studied in the unit in cancer. In general the proposed experiments describe are achievable, but not overly ambitious. The rationale for studying the Dnmt3b hypomorphic allele to cancer is not clear. That DNA methylation is involved in cancer is not in doubt, and the roles played by the different DNMTs in cancer has been intensively investigated. Given the very large amount of research that has already been carried out on this general topic, exactly how these experiments will move the field forward is not clear. Similarly, while it seems very likely that KMTs play an important role in tumourigenesis, the specific aims of this part of the proposed work need to be better defined.

Conclusion

• Overall opinion of the theme:

In general the group are becoming internationally known and are beginning to put out papers and get grants. The very high morale amongst the staff, students and postdocs is notable and the PIs should be congratulated on having created a place where people really want to come and work. During the previous 5 years as a unit they have not published very well in this theme, and hopefully having become established in the new lab space this will now change. There is room for improvement but the groups are well on their way to creating a highly successful research unit.

• Strengths and opportunities:

The main strength of the unit in terms of theme 2 is the breadth of expertise in different developmental systems and tumour models. The group is studying a range of different mechanistic systems, including readers of DNA methylation, writers of histone methylation, and protein phosphatases. This breadth of expertise is a very impressive strength for such a small unit.

• Weaknesses and threats:

Many of the research plans, as presented, lack in focus. Also, there is notable disparity in funding and scientific output amongst groups. While some variability is of course inevitable, it can become problematic when so pronounced.

• Recommendations:

It is highly recommended that peer-to-peer mentoring is implemented within the unit. This could take the form of periodic retreats for PIs where future plans are critiqued amongst the group. Grant applications, manuscripts AND cover letters should also be reviewed and critiqued amongst the group to maximise the chances of a successful entry into and ride through the review process.

5 • Conduct of the visit

Visit dates:

Start: 23th january 2013 at 8.30am

End: 24th january 2013 at 4pm

Visit site(s): UMR7216, Epigénétique et Destin Cellulaire

Institution: CNRS/université Paris-Diderot

Address: Bâtiment Lamarck, 35 rue Hélène Brion, 75205 Paris cedex 13, France

Specific premises visited:

The committee appreciated the short visit of the laboratory that was initially not planned.

Conduct or programme of visit:

The visit was structured as following :

Day 1

Welcome of the committee and first closed-door committee meeting with the AERES representative to discuss the aims and the organisation of the visit.

Short presentation of the AERES role and procedure by the AERES representative and presentation of the committee members to all the participants.

General presentation of the Unit by the Director (20 min talk + 20 min discussion)

Inroduction to Theme 1 by the Theme Manager MrJonathan WEITZMAN (10 min talk + 10 min discussion) followed by the presentations of the group leaders involved (15 min talk + 15min discussion) explaining their main achievements and their objectives.

Inroduction to Theme 2 by the Theme Manager Ms Valérie MEZGER (10 min + 10 min discussion) followed by the presentations of the group leaders involved (15 min talk + 15 min discussion) explaining their main achievements and objectives.

These presentations were a good complement of the documents provided.

A poster session was organized during lunch time with posters from all the groups presented by the PhD students and post-docs. This session and lunch time was a very good opportunity for the committee to meet informally with the lab members.

Second closed door committee meeting with the AERES representative to discuss the presentations of the day, to agree on the overall opinion of the themes presented, to identify the strengths and opportunities, to discuss the weaknesses and threats and to provide recommendations.

Day 2

Discussion with the representatives of the governing bodies (1 hour)

This was followed by short meetings of 20 min each with :

– engineers, technicians and administrative staff

- staff scientists and lecturers

- students and post-docs

- Discussion with the Directors of the unit to discuss specific issues in detail

Last closed-door committee meeting to continue the evaluation and discussion started at the end of day 1 and to organise the writing of the report. This concluded the visit of the unit.

Specific points to be mentioned: (unexpected events, etc.)

The committee wants to thank the Directors and the different groups for the excellent preparation of the visit. The written documents were very good and the presentations and poster session perfectly complemented the documents. This allowed the committee to have all the required information in hand for a faithfull and efficient evaluation based on a less common theme-by-theme analysis.

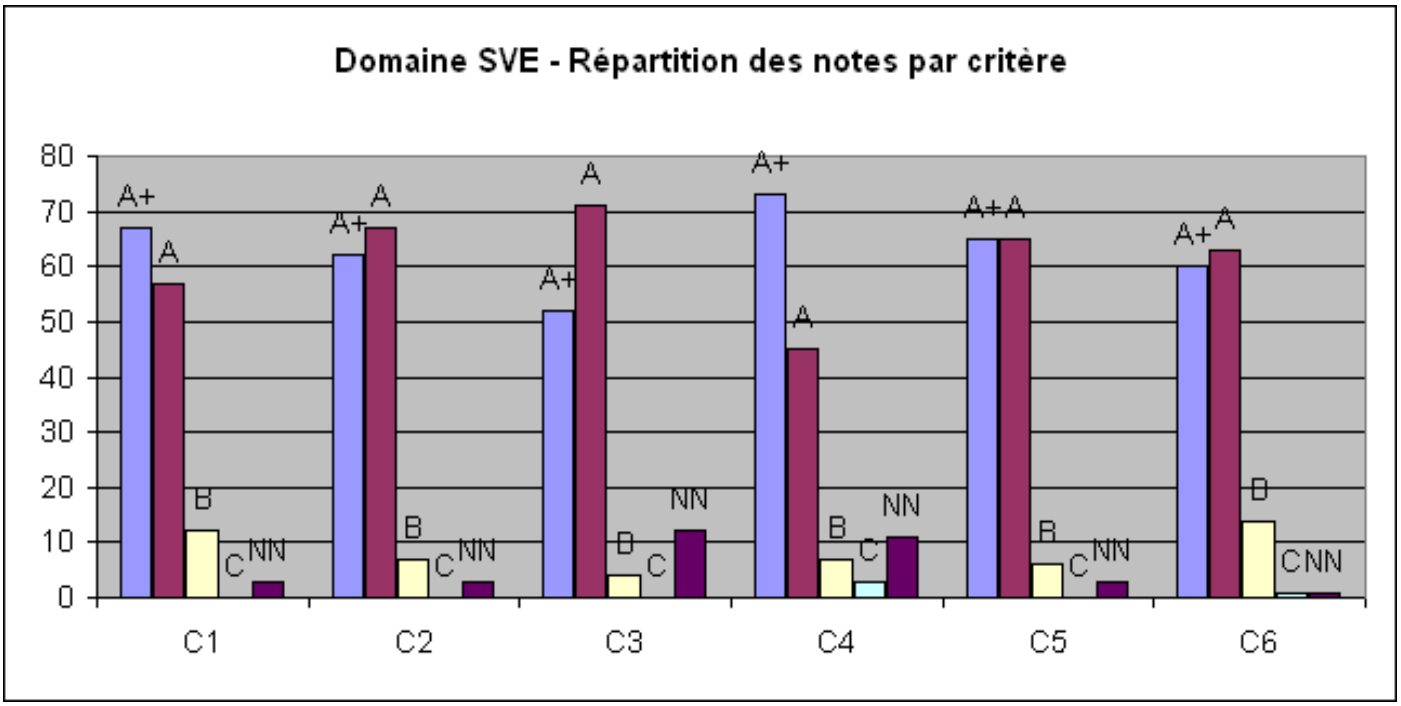
6 • Statistics by field: SVE on 10/06/2013

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%



7 • Supervising bodies' general comments

Le Président

P/VB/NC/YM – 2013 - 110
Paris, le 24 avril 2013

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

S2PUR140006424 - Epigénétique et Destin Cellulaire - EDC - 0751723R

Monsieur le Directeur,

Je vous remercie, ainsi que les membres du comité de visite, pour l'envoi du rapport d'évaluation concernant le « Laboratoire Epigénétique et destin Cellulaire», rapport qui souligne l'excellence de la qualité de la recherche qui est produite, attestée par le haut niveau qualitatif et quantitatif des publications, tant au niveau national qu'international.

Je me réjouis également que le comité signale l'excellent environnement scientifique en terme de plates-formes techniques, et le soutien de cette unité que l''Université apporte grâce au recrutement de personnel technique, constituant l'un et l'autre une aide à la recherche pour cette unité de haut niveau.

Enfin, le directeur du laboratoire soulève, dans sa réponse, la question des surfaces disponibles, considérées comme un facteur limitant pour le développement de l'unité. Nous sommes conscients que les institutions doivent fournir plus d'espace afin d'atteindre une masse critique et de maximiser les synergies et l'établissement tiendra compte, à la hauteur de ces moyens, de cette remarque.

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

Vincent Berger

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SORBONNE PARIS CITÉ
RECHERCHE ENSEIGNEMENT SUPÉRIEUR

Paris, 7th April 2013

AERES Evaluation of the UMR7216 Epigenetics and Cell Fate

The members of the UMR7216 Epigénétique et Destin Cellulaire thank the Chairperson and all the members of the Expert Committee for the time they invested in evaluating our work and our research unit. We are grateful for their professionalism during the site visit and for their useful comments and suggestions.

We are grateful that the Committee appreciated the dynamic atmosphere that we have created and the quality of our scientific achievements. In particular, the report emphasizes our high potential, our dynamic management organisation and our successful positioning nationally and internationally, in a relatively short period of time. We are also grateful that the Committee recognized our investment in high-level recruitment and our integration into local and international research networks. We thank the committee for their suggestions about how to continue to build critical mass for the scientific teams and to strive for ambitious, yet focused, research objectives.

The Committee admired our 'pioneering' decision to structure the Unit in terms of two broad Scientific Themes which underlie emerging strengths and expertise. The report emphasized how this structure has contributed to a coherent and dynamic, interdisciplinary research environment :

- **Theme 1: Epigenetic Mechanisms**: We thank the Committee for recognizing the high quality of the achievements in this field and our investment in developing tools and platform expertise. We will endeavor to continue to build the size and resources of the teams as recommended in the report.
- **Theme 2: Physiopathology in Development and Disease**: We thank the Committee for highlighting the impressive breadth of expertise in a range of developmental systems and tumor models. We acknowledge the need to keep these projects focused and reduce disparity in resources between the teams.

Concerning the general recommendations:

- We agree fully on the importance of group leaders' retreats and we will continue to hold these regularly.
- We will continue to develop peer-to-peer mentoring and to support all teams in their efforts to develop and secure funding nationally and internationally.

- We note the recommendation that additional lab space is crucial for the future development of the unit and our research program.
- We also note that recruitment of bioinformatics expertise and additional administrative support should be priorities in the near future.

We have included a short list of factual corrections.

Once again, we thanks the members of the Evaluating Committee.

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