THeGepi - Thérapie génique, génétique et épigénétique : des maladies rares aux maladies communes en neurologie, endocrinologie et développement

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Gene Therapy, Genetics and Epigenetics in Child Neurology, Endocrinology and Development

GENOSUD

Under the supervision of the following institutions and research bodies:

Université Paris-Sud

Commissariat à l'Énergie Atomique et aux Énergies Alternatives

Institut National de la Santé Et de la Recherche Médicale - INSERM

February 2014

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

Department for the evaluation of research units

On behalf of AERES, pursuant to the Decree of 3 november 2006[1]*,*

- Mr. Didier HOUSSIN, president
- Mr. Pierre GLAUDES, head of the evaluation of research units department

On behalf of the expert committee,

- Mr. Xavier JEUNEMAITRE, chair of the committee

[1] The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n ° 2006-1334 of 3 November 2006, as amended).

Evaluation report

This report is the result of the evaluation by the experts committee, the composition of which is specified below.

The assessment contained herein are the expression of independent and collegial deliberation of the committee.

Unit name:	Gene Therapy, Genetics and Epigenetics in Child Neurology, Endocrinology and Development
Unit acronym:	GENOSUD
Label requested:	UMR_S, CEA
Present no.:	
Name of Director (2013-2014):	Mr Pierre BOUGNÈRES
Name of Project Leader (2015-2019):	Mr Patrick AUBOURG

Expert committee members

Chair: Mr Xavier JEUNEMAITRE, Université Paris Descartes

Experts:

Mr Enrico BERTINI, Children's Research Hospital, Roma, Italy

Mr Juan BUEREN, Centro Investigaciones Energéticas, Medioambientales y Tecnológicas, Madrid, Spain

Ms Isabelle LOUBINOUX, INSERM, Université Paul Sabatier, Toulouse (representative of INSERM)

Scientific delegate representing the AERES:

Mr Laurent GROC

Representatives of the unit's supervising institutions and bodies:

Mr Etienne AUGE, Université Paris-Sud

Mr Alix DE LA COSTE, CEA

Ms Laurence PARMANTIER, INSERM

Mr Michael SCHUMACHER (representative of doctoral school n°419 « signalisations et réseaux intégratifs en biologie (bio-signe) »)

1 • Introduction

History and geographical location of the unit

As a preliminary consideration the experts committee has been evaluating a process of merging the efforts of two separate INSERM units, one led by Mr Pierre BOUGNÈRES and Mr Patrick AUBOURG and the other one by Ms Judith MELKI to create a novel research unit denominated GenoSud. This project is supported by the idea that the integration of 3 research units will provide an added value for potentiating research development by increasing interdisciplinarity. The team 1 has mostly developed cutting edge gene therapy for metabolic and genetic disorders affecting central nervous system; the team 2 has developed epigenetic and environmental research in the field of autoimmune Type 1 diabetes of childhood onset, and the team 3 has a worldwide known experience in genotyping for the discovery of new genes and of new phenotypes. During the visit, the experts committee could perceive the strong support of the local institutions for the creation of this research unit. Université Paris-Sud is very supportive since this research unit represents a bridge between medical research and more fundamental research that will be performed in a project called "Université Paris-Saclay" merging 3 universities and Engineers Schools. In addition, another team is working on gene therapy at this campus, thus increasing the critical mass on this topic and the possibility of collaborations with the unit. The Faculty of Medicine is also very supportive since teams of this research unit are headed by Medical Professors who are fully integrated in the Faculty. They are also critical – especially team 3 – for the structuration of a genetic platform at the Hospital level. The MirCEN structure (70 % CEA, 30 % INSERM) hosts three research teams plus other academic and non-academic (pharma industry) laboratories. Despite formal links with Genethon, no strong research programme is established with this structure. MirCEN is very supportive of the creation of the research unit taking into account its strong activity on gene therapy and adeno associated viruses.

Management team

The unit is headed by Mr Patrick AUBOURG who obviously has the stature and has recognition from all team members. The management seems very good with regular meetings between heads of each research team and also between researchers.

AERES nomenclature

SVE1-LS5 Neurobiology

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	9	9
N2: Permanent researchers from Institutions and similar positions	7	7
N3: Other permanent staff (without research duties)	3	3
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	7	7
N6: Other contractual staff (without research duties)	1	1
TOTAL N1 to N6	**27**	**27**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	8	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	6	
Number of Research Supervisor Qualifications (HDR) taken	13	
Qualified research supervisors (with an HDR) or similar positions	4	4

2 • Assessment of the unit

Strengths and opportunities related to the context

The experts committee has identified several strengths and opportunities that are listed below:

- the creation of this research unit is undoubtedly a nice opportunity for both the research teams themselves, and the institutions (INSERM, CEA, Université Paris-Sud);

- the strengths of each team: (I) expertises on gene therapy for team 1, epigenetics in type 1 diabetes for team 2, gene identification for team 3; (II) originality of the research projects, i.e. not performed in a concurrent research team in France;

- the new unit merges three research teams that should bring an added value for potentiating research development by increasing interdisciplinarity;

- complementary research between clinical paediatric endocrinology research performed at the hospital, genetic research performed also at the hospital and experimental gene therapy research performed in the MirCEN facilities;

- the integration of the INSERM-CEA platform with 7 technicians and engineers for primate studies reinforces the feasibility of the projects elaborated by team 1 using monkeys.

Weaknesses and threats related to the context

The experts committee has identified several potential weaknesses that are listed below:

- location of the research teams in two sites: the INSERM building of Kremlin-Bicêtre hospital and MIRCen Building of CEA Fontenay-aux-Roses. This does not facilitate the interaction between teams 1 and 2 on the one hand and team 3 on the other hand;

- there is heterogeneity of the research themes amongst the three research teams;

- possible lack of feasibility of the research programmes, especially on epigenetics and environment on large populations.

Recommendations

The experts committee has overall an excellent opinion about the project of the unit creation, with several prominent projects that will continue the outstanding scientific level of the researchers. The combination of the three teams will favour additional interactions and foster potential creativity.

3 • Detailed assessments

Assessment of scientific quality and outputs

The three teams composing this new research are all well-recognized at the international level. Team 1 researchers are world-wide acknowledged, especially because of their pioneering gene therapy studies onleucodystrophies. The group leader of team 2 is a very well know physician and scientist, his career being devoted to paediatric endocrine disorders, especially type 1 diabetes. He was the head of the former INSERM unit 946 which is the basis of this new research unit. The group leader of team 3 is also a very well know scientist with a solid experience in molecular genetics, especially with the discovery new genes and functions responsible for motor neuron disease and axonopathies. Another researcher of that team has made very important contributions on the molecular genetics of inherited endocrine and bone disorders (acrodysostosis, hyper-hypo-parathyroidism in particular). Specifically, the team 1 has 36 publications (Science 2009; first and last author) related to the FIRST clinical trial using lentiviral vectors for a monogenetic disease (adrenoleukodystrophy -ADL). Participation in a second gene therapy trial of Beta-thalassemia patients using lentiviral vectors (Nature 2010). Journals of IF ≈10 : Am J Hum Genet, Blood, Brain, etc. It can be noted that one paper is in positive revision in Nature Medicine, two other papers in preparation to be submitted in top-ranked journals. In addition, the team has three patents. For team 2, if the analysis is restricted to the group working on the genetics and epigenetics of type 1 diabetes (T1D), they published 9 papers in which the group leader appears as a first or last author in the last 4 years, among them publications in PLoS One 2013, 2012, and Mol Cell 2012. However, one may note the low number of publications in top-ranked journals in this period. Finally, the team 3 has excellent publications (Hum Mol Genet 2013, 2012; Am J Hum Genet 2012; NEJM 2011) and the group leader, as well as other permanent researchers, participates to the organization of International Congresses (2009, 2010). Altogether, the unit production, although not formed as a whole during the past 5 years, is rather excellent.

Assessment of the unit's academic reputation and appeal

As indicated below in more details, each team leader is well recognized. The head of the unit has pioneered HSC gene therapy with integrative lentiviral vector applied to adrenoleukodystrophy. He was also awarded Grand Prix de l'Académie des Sciences in 2010; a permanent researcher in team 1 also received an Award from the American Society of Human Genetics. They have been invited for conferences in well-known institutes (USA, Europe, Japan). The group leader of team 1 created the European Adrenomyeloneuropathy (AMN) consortium. More recent accomplishments have been made by another researcher of the team for advancing the preclinical gene therapy of inherited forms of Alzheimer disease. The group leader of team 2 is a well-recognized leader in diabetes and endocrine paediatric disorders. One researcher of the team is Emeritus Professor of Epidemiology and Statistics, member of the French Academy of Sciences, expert also in biomathematics, and has obtained several French prizes. They have regular invitations in international congresses, but no recent international awards. To note, one researcher was recently hired by the INSERM within the team. Finally, the group leader of team 3 is a very well-recognized international scientist in human genetics. She has discovered new genes and new functions responsible for motor neuron disease and axonopathies. Another researcher in the team is also internationally recognized and has recently contributed to elucidating the molecular mechanisms of acrodystosis. Their team has strong links with Patients association, through The National Reference Center for rare diseases. The researchers have been invited to two Gordon Conferences, and four post-docs have been recruited within the last 4 years. Altogether, the unit academic reputation is simply excellent.

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

The group leader of team 1, together with a permanent researcher of the team, are principal investigators of international projects (FP7 EU), 4 ANR, 2 PHRC. In addition, they have over 10 contracts in private financing (French and European associations, or networks). The group leader has created the European AMN consortium. The group leader of team 1 and 2 lead a clinical USA-Europ trial in Childhood Cerebral Adrenoleukodystrophy (CCALD) with a biotech company BlueBirdBio (USA) starting in 2013. They also share 3 patents and 6 private research contracts from patients Associations. They also develop a start-up company on gene therapy "AAVLIFE". The group leader of team 2 is the principal investigator of 2 ANR grants, a third one is hold by a researcher of the team. He is also partner of 4 PHRC grants, showing the dynamism of this group in translational research. This team interacts with patients associations on diabetes type 1 (DT1). Over the last 10 years, the team has recruited a large cohort of DT1 patients, allowing genetic and epidemiological research. Finally, member (Ms Alexandra BENACHI) of team 3 is leading a Reference Center for rare diseases, namely congenital diaphragmatic hernia with strong interactions with patients

associations. She also participates to two ANR and two PHRC research programs. Altogether, the unit academic reputation is, once again, simply excellent.

Assessment of the unit's organisation and life

The research unit is set-up on two sites: Hôpital Kremlin-Bicêtre and MiRCEN at the CEA (Fontenay-aux-roses). They use usual laboratories and offices. Importantly, in order to ease the communication between sites they actively use video-conferences, with a global positive outcome. They also run classical lab meetings. The team 1 is working on two sites, i.e. Hôpital Kremlin-Bicêtre for the clinical and genetic human research and MiRCEN at CEA for the experimental studies, especially in primates. The CEA-INSERM MiRCEN provides a high quality environment for monkey research. The team 2 has its research activity mainly based at the Hôpital Kremlin-Bicêtre, where they developed strong and historical interactions with team 1. For instance, the group leader of team 2 is co-director of the CAH gene therapy program developed by team 1. The team 3 is somehow splitted in two sub-projects “team 3A and team 3B”, both headed by well-recognized researchers on genetics and endocrine disorders. They are using the same genetic tools and genetic facility recently built at Hôpital Kremlin-Bicêtre. However, because of different kind of pathologies, they seem to act independently rather than in synergy. Both are working at the site of the Hôpital Kremlin-Bicêtre, in which interactions with team 1 & 2 will certainly be needed to improve integration along the years. Meetings with the students, technical personal and permanent researcher gave an overall positive outcome of the unit strength and planned-cohesion.

Assessment of the unit's involvement in training through research

The unit members are well-integrated into the teaching at the university, with a strong implication in fields such as gene therapy. Team 1 is heavily involved in research and training, e.g. biotherapy teaching program at the Human Genetics Magister of Universities Paris 5 and 7. They organized the Annual Congress of the European Society for genes and cell therapy in 2012. They co-direct the Therapeutic Innovation and Translational Research teaching program at the local doctoral school. This team participates to 6 masters, and along the last 4 years 3 thesis were obtained, 3 thesis on going, and 7 master students were trained. The participation of team 2 is relatively more modest although they had one thesis obtained and one ongoing. Team 3 participates to university teaching in 4 different masters, and during the last 4 years, they had one 1 thesis obtained and 2 ongoing. The meeting with the head of the representative of the doctoral school to which most students are affiliated (École Doctorale n°419 "Signalisations et Réseaux Intégratifs en Biologie") gave a very positive and enthusiastic impression of the unit implication in training.

Assessment of the strategy and the five-year plan

The project is overall original because it assembles together team 1 that is developing cutting edge therapies in the challenging field of neuroscience and particularly to tackle disorders of the central nervous system with team 2 and team 3 that has a solid background in the characterization of new genes and its functional implications. More specifically, team 1 considers that AAV-gene therapy will become a potent tool for the gene therapy of specific diseases, such as the ones they are currently considering. They will test a new lentiviral vector with improved transduction efficacy in ALD. The french gene therapy trial will be opened in New York in metachromatic leukodystrophy (MLD). Other programs will be launched such as the optimization of the intra-thecal delivery of AAV in monkeys in AMN, studies in large animal models and clinical trials in FA (Friedreich cardiomyopathy), and CAH (congenital adrenal hyperplasia), studies in small animal models in inherited AD, and HD (Huntington disease). Team 2 has an ambitious and program on epigenetics of type 1 diabetes with original strategies modelling the child’s lifetime through a geographical approach and life-style questionnaires and measuring epigenetic changes as well as other epidemiological parameters (pregnancy-child). This team needs to be reinforced to get more chances to get significant original results. Team 3 projects mainly rely on the identification of genes and genetic variants with WES that will be completed by functional experiments in mouse and zebrafish models, as well as cellular models. This team has access to unique resource of orphan diseases.

Overall, the experts committee agrees that the coordination of this complex project is well led by a clinician/researcher with expertise in the development of cutting edges therapies, including gene therapy, because this represents the final step of the translational research pipeline. However, the diversity of projects and strategies may make difficult real efficient interactions between the teams.

4 • Team-by-team analysis

Team 1: Multi-disease gene therapy

Name of team leader: Mr Patrick AUBOURG

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	2	2
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)	2	2
N4: Otherprofessors (PREM, ECC, etc.) PU-PH, PR, MCF, PH		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	4
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**10**	**11**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	5	
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

The team is world-wide acknowledged because of their pioneering gene therapy studies and clinical trials on two devastating leucodystrophies: cerebral adrenoleukodystrophy (ALD) and metachromatic leukodystrophy (MLD). Additional interests of this team are focused on inherited forms of Alzheimer disease (AD), Friedreich ataxia-cardiomyopathy (FAC), Adrenomyeloneuropathy (AMN) and Congenital Adrenal Hyperplasia (21-OH-deficiency).

ALD: the internationally pioneering work of this team on ALD gene therapy, allowed them to publish in Science in 2009 the first results of their gene therapy trial with lentiviral vectors. It is expected that further studies, mainly related with the analysis of the pattern of integrated copies of the LVs, will be published soon in good scientific journals. In addition to gene therapy, this team aims to elucidate genetic and epigenetic factors that modulate the ALD phenotype.

MLD: for MLD this team has developed a gene therapy approach based on the intracerebral injection of adeno-associated viral (AAV) vectors expressing arylsulfatase. The proof-of-concept observations in small animal models have been already published by this group, and data from large animal models will be submitted soon. Interestingly, a clinical trial has been opened very recently and is under evaluation to be opened in New York in collaboration with Mr Ronald CRYSTAL.

Inherited AD: because cholesterol regulates the production and clearance of Aß-peptides in neuronal cell lines and it is increased in the brain from AD patients, this team has proposed to enhance its degradation by the overexpression of the *CYP46A1* gene. The proof-of-concept of the efficacy of this novel approach has been published by this team in 2010 using AAV vectors delivered to the brain of a mouse model of AD.

From a total of 36 papers published since 2009, this team has an outstanding publication record with 1 ground-breaking paper (Science 2009; first and last author) related to the FIRST clinical trial using lentiviral vectors for a monogenetic disease (ALD. In addition, this team participated in a second gene therapy trial of Beta-Thalasemia patients using lentiviral vectors Nature (2010). Overall, the experts committee evaluates the scientific quality and outputs asoutstanding.

Assessment of the unit's academic reputation and appeal

As a consequence of the pioneering gene therapy clinical trial on ALD patients, there has been a recognition of the team leaders in several different Academias. Mr Patrick AUBOURG: Grand Prix de l'Académie des Sciences in 2010; Ms Nathalie CARTIER: American Society of Human Genetics, among other awards. Concerning national and international grants, the team has funding from France, from the European Commission (FP7) and also from US companies. Most of them are led by the group leader and one of the team researchers. One researcher of the team was the President of the 2012 meeting of the European Society for Cell and Gene Therapy. Many other distinctions were made to members of the team, including 3 student awards. The team members gave several lectures as invited speaker at the international level (17 presentations in meetings, 9 lectures in US, EU and Japan). The team members are members of several scientific committees and the group leader is in the editorial board of Gene Therapy Journal.

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

Clinicians working in the laboratory are involved in the care of the patients and families at the National Rare Disease Center for Leucodystrophies, a part of the clinical Neuropaediatric unit headed by the team leader. The team will expand this LV-HSC gene therapy approach of CCALD in a new US-Europe Phase III trial starting end of 2013 and plan to use a more potent LV vector provided by the biotech company BlueBirdBio (USA).They have created a start-up AAVLife to speed up preclinical steps towards a clinical trials in 2016 for FRDA cardiomyopathy (Inserm-Transfert and Inserm-Transfert-Initiave). The team plans to establish the necessary collaborations with biotechs and academic labs to be able to use improved AAV vectors at a GLP level in large animals. The team has obtained 6 grants from patients Associations. The group leader has obtained industrial partnerships with BlueBirdBio. The team has also obtained three patents related to the treatment of diseases mentioned above. All these activities reflect a strong commitment of the team with the Social and Economic environment.

Assessment of the unit's organisation and life

A potent gene therapy group has been already installed at the MIRCEN Institute at CEA-Fontenay to facilitate the studies performed with monkeys housed in CEA-INSERM, and collaborations with the neuroscience equipment of the MIRCEN Institute and the heart surgery facility of CCML. These strategic decisions to combine clinical units, research units and platforms should result in the development of optimized gene therapy of the neural diseases considered by the authors. It is of significance that this team will interact with the other two teams of the unit in the CEA-INSERM platform.

Assessment of the unit's involvement in training through research

The team participates in the Biotherapy teaching program at the Human Genetics Magister of Universities Paris 5, Paris 7, and is involved in the Therapeutic Innovation and Translational Research program. Both the group leader and one researcher teach in biotherapy and neuroscience in 6 masters. Three thesis were presented during the last 3 years, and three others are currently undergoing. The team is thus very well implicated in the training of young researchers, i.e. 6 PhD students, 7 Master students, and 4 post-docs. Taken together the training track of the team can be considered extremely positive.

Assessment of the strategy and the five-year plan

This team has considered that AAV-gene therapy will become a very efficient and safe tool for the gene therapy of specific diseases, such as the neural diseases they are currently considering in their preclinical and clinical work. The decision of moving from the hematopoetic lentiviral gene therapy approach to a direct CNS administration of therapeutic AAV vectors constitutes a very relevant decission which hopefully will keep this team as international leaders in the definition of the most efficient approaches for the treatment of neural diseases. The team also aims that Université Paris-Sud and School-of-Medicine should be Reference Centers in this respect.

Plan for the specific gene therapy approaches in the following years:

- ALD: the team plan to expand the LV-HSC gene therapy approach of ALD in a new US-Europe Phase III trial using a more potent LV vector provided by BlueBirdBio. Because of limitations of current LV vectors used for the gene therapy of ALD patients only modest transduce of CD34+ cells have been achieved. A new LV with improved transduction efficacy will be investigated first in experimental studies;

- MLD: the gene therapy trial already opened in France will be also proposed to be opened in New York;

- AMN: the team plans to optimize the intra-thecal delivery of AAV in monkeys to define the vector dose to be used in AMN patients, with the final purpose of conducting a clinical trial in France and in the US;

- FA: aims will be focused on the treatment of myocardium since a high proportion of these patients die from cardiac failure. Frataxin-AAV vectors will be proposed for these gene therapy studies which will be conducted in collaboration. Studies in large animal models and clinical trials will be conducted in the near future;

- CAH: affected women in adult life due have a very severe and chronic virilisation. Preliminary results have shown that intra-adrenal injection of AAV vector carrying the gene that encodes the hydroxylase enzyme deficient in CAH patients corrects the phenotype in a mouse model of disease. Once the studies will be conducted in large animal models, clinical trials would be proposed;

- Inherited AD: the team will investigate the effects of intracerebral injection of AAVs expressing the CYP46A1 in mouse models of the disease. Because intracerebro-ventricular injection of AAV2 vector has a limited diffusion capacity, new AAV serotypes with improved properties will be used in mouse and monkey models;

- HD: based on recent evidences suggesting that cholesterol homeostasis is impaired in HD, the authors observed a down regulated expression of CYP46A1 both in mouse and human HD. From a collaboration with neuroscientists in Paris (CNRS, Université Paris 6) they observed that the re-restored expression of this gene in a mouse model of the disease improved the characteristic motor deficits. In this collaborative effort, the implications of the overexpression of CYP46A1 on the phenotype of HD mice will be further investigated.

Taken together, a very ambitious strategy of high quality experimental and clinical research has been planned by the team for the next 5 years of work.

Conclusion

- **Strengths and opportunities:**

This team is one of the pioneering international leaders for the gene therapy of neural diseases. So far they have used LVs in their clinical trials, and now they are planning to move towards the use of AAV vectors for the treatment of different neural disorders, both genetic and acquired.

This team investigates the safety and efficacy of different gene therapy strategies in relevant animal models, progressing towards the development of clinical trials.

The long-term experience in bringing this kind of therapies to the clinic lets no doubt that this multi-disease program is very ambitious, but also realistic.

- **Weaknesses and threats:**

The complexity and the large number of diseases to be considered in the next years would imply a risk of diluting the efforts among all these objectives.

Because the CNS administration of AAV vectors constitutes a new gene therapy approach in the clinics, this impliesnew risks related with the administration route and the toxicity of the vector. However this risk seems to be very well evaluated by the team, based on the very pertinent toxicity studies conducted in relevant animal models.

- **Recommendations:**

Continue with the very well-coordinated preclinical and clinical work in selected neural diseases; prevent delays in the publication of the very relevant work already conducted in both the preclinical and clinical gene therapy studies to maintain the novelty of these results.

Team 2: Epigenetics, gene-environment studies in childhood autoimmune diabetes

Name of team leader: Mr Pierre BOUGNÈRES

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	3	3
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	2
N6: Other contractual staff (without research duties)	1	1
TOTAL N1 to N6	**10**	**9**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs

The team head is a very well know physician and scientist, his career being devoted to paediatric endocrine disorders, especially type 1 diabetes. The group leader was the head of the former INSERM unit 946 composed of two teams. During the last 4 years, the group leader's unit has published well. If we restrict the analysis to his group working on the genetics and epigenetics of type 1 diabetes (T1D), they published 9 papers in which the group leader appears as a first or last author in the last 4 years, among them publications in PLoS One 2013, 2012, and Mol Cell 2012. However, one may note the lack of publication in top-ranked journals in this period. The group has performed an original work on epigenetics in type 1 diabetes. A strong effort has been made setting-up ahome-mademethylome array especially by a young researcher in the team. This has allowed to study CG methylation marks in the INS and IL2RA genes showing the possible importance of epigenetic changes at these genes in T1D. A whole methylome approach is now performed. Whereas this approach could lead to original findings, the demonstration of marginal and

multiple epigenetic effects on T1D will probably require large populations and replication studies in order to be better published. The large cohorts initiated by the group leader and a researcher will help in that regard. Overall, the scientific quality and outputs should be considered as excellent.

Assessment of the unit's academic reputation and appeal

There is no doubt on the international reputation and appeal of the group leader in diabetes and endocrine paediatric disorders. One researcher of the team is Emeritus Professor of Epidemiology and Statistics, member of the French Academy of Sciences, expert also in biomathematics, and has obtained several French prizes. There is no doubt also that both the group leader and researchers of the team can synergize to propose new original protocols and strategies on epigenetics of diabetes. Both have been invited to give some international lectures. This is the last 5-year contract position headed by the group leader and no middle-aged researcher working in epidemiology and biostatistics is part of the group, one being more a molecular biologist and geneticist. This relative weakness may hamper the production of innovative results in the near future. No foreign post-doc has been attracted by the group in the last years. Overall, the academic reputation and appeal was considered as fully satisfactory.

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

The group leader is the head of a Pediatric and Endocrinology Department at the Hôpital Kremlin-Bicêtre (Paris). The team has a strong clinical research activity. The group leader is the principal investigator of 2 ANR grants, a third one is headed by a researcher now in another team. Four PHRC grants, showing the dynamism of this group in translational research. The group leader has also fostered interaction with patients associations on diabetes type 1 (DT1). Over the last 10 years, the team has recruited a large cohort (n = 7000) of DT1 patients, allowing genetic epidemiological research. Interaction with this population through auto-questionnaires investigating lifestyle and environment exposures, allowing the study of gene-environment interaction and modelling the child's lifetime through a geographical approach. The team has industrial contract with NovoNordisk (epidemiology of childhood T1D). This activity is simply excellent.

Assessment of the unit's organisation and life

The team has been assembled recently, focusing on the Epigenetic program of the group leader former INSERM unit. The activity of this research group is mainly based at the Hôpital Kremlin-Bicêtre since their move from the Hôpital St Vincent de Paul (Paris Descartes) in 2012. There have been long-term interactions with the team 1 and its group leader. For instance, the group leader of team 2 is co-director of the CAH gene therapy program developed by team 1. Clinical and genetic interactions with team 3 should be facilitated by the presence of a researcher both in teams 2 and 3. It will be critical to organize weekly meetings between the different teams to ensure a real research unit's life.

Assessment of the unit's involvement in training through research

During the last 4 years the team has been involved in teaching with: 1 thesis obtained, 1 thesis ongoing, and 3 post-doctoral fellows. The participation in training at university is through the participation to a Master.

Assessment of the strategy and the five-year plan

The activities of the team will be focused on epigenetic research, more specifically with studies of CG methylation of DNA, with the objective of finding methylation marks associated with T1D and gene-environment interactions (response to a stress or a treatment). At the epidemiological level, this an original project trying to modelize the child's lifetime through a geographical approach and life-style questionnaires and to measure epigenetic changes as well as other epidemiological parameters (pregnancy-child). At the cellular levels, experiments are conducted to measure epigenetic changes by glucose exposure in several cell lines. First interesting preliminary data have been obtained. Measurement of epigenetic marks and methylome in blood white cells from T1D patients will be of interest but will have also the limitation of the tissue specificity of epigenetic changes. However, this sophisticated epigenetic research program appears somewhat isolated – not in terms of research theory or conception but rather in the connection with other large similar cohorts. A more active search for collaborations within this field would probably be fruitful on the long-term.

Conclusion

- **Strengths and opportunities:**

Innovative research program on epigenetics of type 1 diabetes.

Recruitment of a large cohort (n > 6000) of subjects witt T1D with a large number of environmental variables allowing gene environment interaction studies.

In house set-up of a small epigenetic platform allowing methylome array technology.

Interesting set up of cellular assay: methylome of BTC3 cells exposed to hyperglycemia.

Original research on the relationship between psychosocial maternal factors and childhood obesity through epigenetic marks (EpiChild program).

Ambitious program (Epimood) aiming at an integrative translational analysis between epigenetic marks, physiology and maternal behaviour for understanding early maternal neglect and mood disorders.

Complementary approaches and close collaborations with team 1.

Genetic collaborations to develop with team 3.

- **Weaknesses and threats:**

Recent move to the Université Hôpital Bicêtre. Thus local collaborations and networking probably need to be reinforced.

Relatively small research team lacking permanent researchers that would enhance the productivity. Need for at least one Engineer in Bioinformatics. In the unit, relative isolation on the field of epigenetics.

Epigenetics is becoming a higly competitive field requiring complete and innovative results for being published in high impact journals. Each research program seems itself ambitious and sometimes overambitious (Epimood for example) for this little research team.

Interesting preliminary results on epigenetic profile performed on white blood cells in young T1D patients but performed on a too small series (n = 10 cases and 10 controls) requiring replication.

Problems of the risk of spurious findings when looking at epigenetic marks at the whole genome level requiring multiple large data sets.

- **Recommendations:**

Taking into account the size of the team, one would recommend focusing on two or three major programs, too much diversity being at risk to not be efficient. This team needs to recruit an Engineer in bio-informatics as well as another full-time researcher to be more efficient.

Team 3: Genomics and pathophysiology of orphan paedratric neuromuscular, endocrine and developmental diseases

Name of team leader: Ms Judith MELKI

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	4	4
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**7**	**7**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	5	
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

The team leader is a very well know scientist with a solid experience in genotyping and in molecular genetics. She has dedicated most of her research carrier to discover new genes and new functions responsible for motor neuron disease and axonopathies. Her scientific production is outstanding and she is very well known internationally. The team will take advantage from this project to empower the collection of well assessed and defined rare clinical phenotypes (collaboration with team 1) with unknown genetic background and to develop functional studies in cells, mouse models, or zebrafish (collaboration within the team 3 and with team 2). Indeed, this team is composed of two subgroups, the one headed by the group leader mainly working on motor neuron diseases, the second one being headed by permanent researchers mainly working rare inherited diseases of mineral and bone metabolism. Both subgroups have been successful independently in the past years.

It is clear that the main activities for genotyping in search of new genes represented by team 3 is quite a challenging and competitive area that will have advantage by a close interaction with groups that develop functional studies by modelling disease mechanisms. The impression reading this proposal is that the strategy and framework of this proposal goes in the right direction.

Assessment of the unit's academic reputation and appeal

Reading the summary of teaching activities in Université Paris 11, and the quality of the post-docs working in the team, the experts committee has the impression that this is a very active and appealing team with a high level of excellence. The scientific production in terms of publications is very good. Moreover the international reputation of the group leader is undoubtedly outstanding beyond her discovery of the SMN gene. The group leader and her team well understand that the simple genetic characterization of new genes in the field of rare diseases needs the integration of both the development of functional studies to have insights on the pathogenesis and very efficient interactions with international networks in order to collect additional patients and families to obtain a higher impact. Reading this project about the accomplishments so far gives a strong impression of a research unit that has a very good international interaction and reputation.

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

The team has produced one patent: methods for predicting, treating and modelling hormone resistance. Overall the team has obtained 7 grants by several agencies (ANR, PHRC, CRC, ERM, AFM) related to motor neuron disease, molecular signatures and function of B lynphocytes, molecular genetic definition of arthrogriposis, and genetic bases of Diaphragmatic hernia. The team has established a very good national network to collect patients with arthrogriposis, Diaphragmatic herni. Moreover, several international collaborations have been established particularly for motor neuron disease, spastic paraplegia and endocrinological disorders of the bone.

Assessment of the unit's organisation and life

Team 3 has been assembled just one year ago in 2013 merging together the INSERM unit led by the group leader with another INSERM unit. Moreover the group leader has moved from Genopole to join the Hôpital Kremlin-Bicêtre and creates team 3 to mostly dedicate energy to advanced genomic activities such as mastering exome and NGS genomics, including bioinformatics. Moving to the Hôpital Kremlin-Bicêtre and to the Université Paris-Sud, and coming together with the other teams will allow the group leader to come closer to clinical activities and to clinicians in order to better tackle the activity of genotype-phenotype correlation for genetic syndromes with unknown genetic background. It will be critical for team 3 to organize annual interviews with engineers and technicians.

Assessment of the unit's involvement in training through research

The team has at least 2 PhDs and 1 Post Doc. Moreover researchers, including the group leader, are actively giving teaching courses for Masters. By the fact that the group leader has moved to the Hôpital Kremlin-Bicêtre and the Université Paris-Sud, teaching courses could potentially be implemented.

Assessment of the strategy and the five-year plan

It is clear that the activities of the team will be focused on the discovery of new genes in the field of rare diseases by the application of NGS methodologies. It is conceivable that in a 5-year plan the simple molecular genetic characterization for new genes or new genotype –phenotype correlation discoveries will turn to be obsolete.

Thus the project to put together team 3 with the other 2 teams that integrate activities/expertise that have an early history and a more extended future, such as epigenetics/environment and gene therapy applied to genetic disorders, seems to be fairly strategic. Thus the weakness of the potentially limited activity of simply accelerating the results of genomic sequencing for the discovery of new disease genes will be compensated not only by the integration and facilitated communication with the other 2 teams but also by the additional role of team 3 in the study of microRNA and RNA microarray analysis.

Conclusion

- **Strengths and opportunities:**

The team is led by a worldwide well-known scientist and geneticist, mostly since her discovery of the gene responsible for Spinal Muscular Atrophy, one of the most frequent recessive autosomal disorders. Furthermore, the group leader and her team are very active in discovering new genes every year.

Moving from Genopole to an university Hospital will surely improve the number of collaborations with clinicians to cover areas regarding the phenotype of rare disorders that are covered by this team.

The team will have the advantages of having a well-equipped laboratory for genomic investigations and advantages by merging with the other teams for the development of functional models.

- **Weaknesses and threats:**

Genotyping for new disease genes is becoming more and more challenging for publishing competitive and high impact papers. Thus on one side this team will have to make an effort in increasing international networks for collecting additional patients and on the other they should implement the development of the different branches of functional genomics.

- **Recommendations:**

Increase and implement the national and international network to improve and speed up the validation of novel disease genes. Besides developing genotyping activity to discover new disease genes, implement the area of functional genomics because there is a risk that genotyping for new disease genes with become obsolete in the next 5 years. For this period, these genotyping activities could profit from a formal collaboration between Université Paris-Sud, INSERM, CEA and the Institut de Génomique / CNG at Evry with very strong massive sequencing capabilities with – among others – Whole Exome Studies and Whole Genome Studies.

It is essential to acknowledge that the team sub-organization, i.e. parts 3a and 3b, requires planning for functional and interaction studies, for example with zebrafish experiments and functional studies in cells and mice. The next 5 years will show if the sub-organization of the team will benefit from the experience and knowledge and expertise in gene therapy and epigenetics of team 1 and team 2.

5 • Conduct of the visit

Visit date:	February 4th 2014
Start:	February 4th 2014 at 8:30 am
End:	February 4th 2014 at 5:30 pm
Visit site:	CEA – MirCEN
Institution:	CEA
Address:	Centre de Fontenay-aux-Roses, 18 route Panorama, 92265 Fontenay-aux-Roses

Specific premises visited:

The experts committee had a dedicated time to visit the laboratory of MirCEN and the CEA-INSERM platform comprising a fully-equiped space for monkey breeding and experimentation, brain imaging studies and neurostructural correlates.

Conduct or programme of visit:

08.30 am	Arrival on-site
08.30-09.00 am	Experts committee discussion (closed door)
09.00-09.05 am	Presentation of the AERES evaluation by the Scientific Delegate Mr Laurent GROC
09.05-09.40 am	Unit presentation by Mr Patrick AUBOURG
09.40-10.20 am	Team 1 Mr Patrick AUBOURG
10.20-11.00 am	Team 2 Mr Pierre BOUGNÈRES
11.30-12.10 pm	Team 3 Ms Judith MELKI
12.10-01.30 pm	Lunch with tutelles and representative of doctoral school
01.30-02.00 pm	Visit Platform
02.00-02.45 pm	Parallel meetings: • meeting with all students/postdocs; • meeting with all ITAs; • meeting with all permanent researchers (without team leaders and unit director).
02.45-03.15 pm	Interview with director
03.15-05.30 pm	Closed-door meeting
05.30 pm	End of the visit

6 ● Supervising bodies general comments

UNIVERSITÉ PARIS SUD

Comprendre le monde, construire l'avenir®

Le Président de l'Université Paris-Sud

à

Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
AERES
20, rue Vivienne
75002 Paris

Orsay, le 3 juin 2014

N/Réf. : 141/14/JB/LM/AL

Objet : Rapport d'évaluation d'unité de recherche
N° S2PUR150007887

Monsieur le Directeur,

Vous m'avez transmis le 12 mai dernier, le rapport d'évaluation de l'unité de recherche « Thérapie génique, génétique et épigénétique : des maladies rares aux maladies communes en neurologie, endocrinologie et développement» - N° S2PUR150007887, et je vous en remercie.

L'université se réjoit de l'excellente appréciation portée par le Comité sur cette unité et prend bonne note de ses suggestions. Elle s'assurera que le projet de cette nouvelle unité se met en place comme espéré.

Vous trouverez en annexe les éléments de réponse de Monsieur Patrick AUBOURG, Directeur de l'unité de recherche.

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

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Le 19 Mai 2014

Observations sur le rapport d'évaluation de l'AERES

Les experts de l'AERES ont analysé dans le détail les projets de recherche de la structure en création (unité mixte INSERM-CEA-Paris11) et l'organisation mise en place pour les mener à bien. Ils ont souligné que la réunion des 3 équipes (P. Aubourg, P. Bougnères, J. Melki) composait un ensemble ambitieux avec une diversité de projets. Le comité a exprimé l'importance de développer les interactions entre les équipes, chacune poursuivant un programme original et spécifique. Ces interactions se sont développées en 2014 au lendemain de la réunion effective des 3 équipes dans un même projet. Les séminaires, réunions de travail, échange de techniques, partage d'expériences sont fédérés par le fait que l'ensemble des équipes emploient des techniques de génétiques moléculaires et s'intéressent au contrôle de l'expression des gènes. Certains programmes sont déjà partagés entre P. Aubourg et P. Bougnères (thérapie génique du bloc en 21 hydroxylase), J. Melki et P. Bougnères (identification de gènes de maladies endocriniennes), J. Melki et P. Aubourg (identification de gènes de maladies neuropédiatriques). Ce qui réunit les 3 équipes est aussi la dimension médicale pédiatrique autour de maladies génétiques de l'enfant. Les 3 chefs d'équipe s'entendent bien et partagent leur vision du futur de l'unité à moyen terme. L'organisation en 2 sites obéit à des impératifs scientifiques. Le site de MIRCen-CEA permet en effet aux équipes de réaliser des projets de recherche (thérapie génique et épigénétique) dans le modèle de primate non-humain et de bénéficier pour cela d'un environnement technologique unique. C'est pour cette raison que la structure s'est constituée avec mixité INSERM et CEA, et une participation active à la vie scientifique et technique de la plateforme MIRCen (Directeur : P. Hantraye). Les 3 chefs d'équipe, mais aussi plusieurs chercheurs participent activement à l'enseignement universitaire, scientifique et médical. L'organisation en 2 sites n'est pas à nos yeux et dans la vie quotidienne un obstacle significatif à la vie scientifique de l'unité. Chercheurs et techniciens s'échangent entre les 2 lieux qui se trouvent ainsi associés dans les mêmes projets. Il s'agit donc ainsi d'une complémentarité que les chefs d'équipe et le directeur de l'unité s'attachent à développer à son meilleur niveau. La présence de l'unité à MIRCen enrichit son champ scientifique et l'accès à la plateforme enrichit le champ technologique de toute l'unité.

Commentaires spécifiques

Team 1. L'équipe 1 s'est engagée dans un programme très ambitieux de thérapie génique adressée à plusieurs maladies. Les experts se sont interrogés sur le risque de dilution des efforts et de l'énergie en raison du nombre qu'ils leur a parut élevé de pathologies abordées. Notre réponse à cette crainte est que l'équipe 1 a développé ces dernières années des approches génériques d'utilisation des virus AAV sur le plan scientifique, technique et réglementaire, ainsi que des partenariats chirurgicaux (cœur-cerveau) très solides. Mis dans un pot commun, ces réalisations permettent d'aborder d'affilée plusieurs maladies à condition d'approprier les outils et les choix des pathologies, ce qui a constitué le fondement de notre stratégie : une plateforme médicale, scientifique, réglementaire et technique applicable à un sous-groupe de maladies bien choisies. Il est également important d'indiquer que l'application des progrès accomplis aux patients s'appuie sur un partenariat actif avec 2 sociétés de biotechnologies, dont l'une a été crée spécifiquement dans cet objectif.

Team 2. Les experts de l'AERES ont noté à juste titre un certain degré de disproportion entre la diversité des sujets abordés dans la recherche en épigénétique humaine et la dimension modeste de l'équipe 2. Il est tout à fait vrai que la mise au point de techniques d'étude de loci candidats mais aussi du methylome entier a ouvert plusieurs champs de recherche dans lesquels l'équipe n°2 s'est engagée. P. Bougnères et D. Fradin sont tout à fait conscients qu'après l'étape technologique, il va leurs falloir concentrer leur recherche sur 2 ou 3 champs bien

circonscrits. Ceci est également vrai de la recherche environnementale conduite dans l'équipe. En 2014, les champs scientifiques abordés se sont plus précisément concentrés.
Les experts ont recommandés le recrutement d'un ingénieur en bio-informatique comme support essentiel au travail de cette équipe. On peut souligner qu'un tel recrutement est évidemment le bien venu et aurait aussi beaucoup d'intérêt pour l'équipe 3, grosse utilisatrice de bio-informatique. La recommandation des experts de l'AERES va donc faire l'objet d'une demande de recrutement.

Team 3. L'équipe 3 a récemment rejoint l'unité constituée par P. Aubourg et P. Bougnères. Les experts de l'AERES s'interrogent sur sa capacité à maintenir un haut niveau de découvertes originales dans la compétition internationale pour ce qui est du recrutement de patients rares et de la génomique fonctionnelle des mutations et des gènes. Ils saluent l'efficacité de l'équipe 3 dans la découverte des mutations de nouveaux gènes. Il est important de leurs répondre qu'aussi bien dans le champ des pathologies abordées par J. Melki que dans celui de C. Silve, des recrutements, réseaux nationaux de médecins, associations de patients, connexions internationales ont été efficacement mises en place par les 2 chercheuses. Ce volet associé à la maitrise des nouvelles technologiques de la génomique y compris bioinformatiques nous semblent être de très bons atouts. Pour ce qui est de la génomique fonctionnelle, l'équipe 3 bénéficie d'une bonne maitrise des systèmes cellulaires d'expression comme d'excellentes collaborations pour les modèles souris et zebrafish. Récemment réunies en une seule équipe, J. Melki et C. Silve ont trouvé un très bonne espace de partage de techniques et de projets.

Bien cordialement

Patrick Aubourg