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

Section des Unités de recherche

AERES report on unit:

Endogenous retroviruses and retroïd elements of higher eukaryotes

RETRO-ENDO

Under the supervision of the following institutions and research bodies:

Université Paris-Sud

Centre National de la Recherche Scientifique - CNRS

Institut Gustave Roussy

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. Philippe ROINGEARD, 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 assessments contained herein are the expression of an independent and collegial deliberation of the committee.

Unit name:	Endogenous retroviruses and retroïd elements of higher eukaryotes
Unit acronym:	RETRO-ENDO
Label requested:	UMR
Present no.:	8122
Name of Director (2013-2014):	Mr Thierry HEIDMANN
Name of Project Leader (2015-2019):	Mr Thierry HEIDMANN

Expert committee members

Chair:	Mr Philippe ROINGEARD, Université François Rabelais, Tours
Experts:	Ms Colette KANELLOPOULOS-LANGEVIN, Inserm, Faculté de Médecine Xavier Bichat, Paris
	Mr Michael KANN, CNRS, Université de Bordeaux (representative of the CoNRS)
	Mr Massimo PALMARINI, University of Glasgow, Centre for Virus Research, Glasgow, United Kingdom
	Mr Didier TRONO, École Polytechnique Fédérale de Lausanne, Switzerland

Scientific delegate representing the AERES:

Ms Catherine SCHUSTER

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

Mr Etienne AUGÉ, Université Paris-Sud

Mr Bruno LUCAS, CNRS

Mr Eric SOLARY, Institut Gustave Roussy

Ms Sylvie VAN DER WERF (Doctoral School N°516 representative)

1 • Introduction

History and geographical location of the unit

The unit, located at the Gustave Roussy Research Institute (IGR) in Villejuif, is a thematically very focused unit whose research subjects are retroelements and retroviruses. Recently, the structure of the unit has slightly changed, with the arrival of a small group of cellular electron microscopists.

Management team

Head: Mr Thierry HEIDMANN

AERES nomenclature

SVE1_LS6, SVE1_LS3, SVE1_LS2, SVE1_LS1

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent researchers from Institutions and similar positions	6	6
N3: Other permanent staff (without research duties)	7	6
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	4	4
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**17**	**16**

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

2 • Overall assessment of the unit

Overall assessment of the unit

The research entity has done in the past and continues to carry out an outstanding research on endogenous retroviruses. This research forms a continuum ranging from fundamental work to more applied aspects, on different physiological and pathological mechanisms. The research entity also develops translational research projects focused on vaccines. Overall the research entity performs an excellent work and its output has been truly remarkable.

Strengths and opportunities related to the context

The research team RETRO-ENDO has an international reputation based on the very high quality of its publications. The research performed is based on a logical sequence of closely related projects. It forms a continuum of fundamental molecular work to physiology and physiopathology. Moreover, the research entity performs an excellent translational research, which led to the creation of a spin-off start-up company and to the development of a veterinary vaccine currently on the market. The team is built around a group of young talented researchers and excellent students.

Weaknesses and threats related to the context

The research entity seems to be isolated within the Gustave Roussy Research Institute and the university. There is a risk that the unit will develop too many different sub-projects with regard to human resources. To date, the emergence of young researchers that could eventually take a leadership in the unit is not visible.

Recommendations

The communication within the unit should be improved, especially with engineers and technicians and the emergence of young researchers who could take a leadership in the near future should be now a priority.

3 • Detailed assessments

Assessment of scientific quality and outputs

The RETRO-ENDO research entity has been at the forefront of research on molecular virology of endogenous retroviruses (ERVs) during the last 15 years, with highly cited publications. During the last 5 years, RETRO-ENDO has made major contributions to the understanding of the role of ERVs in reproductive biology of mammals. The research team has discovered a variety of ERV-derived genes encoding proteins named syncytins; this was a major contribution to the understanding of the overall influence of ERV envelope (Env) genes on mammalian placentation. Syncytin knock-out mice demonstrated unambiguously the role of these genes in placentation and formation of the two-layered syncytiotrophoblast in the murine placenta.

The team also demonstrated that Env proteins of retroviruses are immune effectors responsible for immune evasion. The immunosuppressive domains (ISD) of the Env proteins of several retroviruses have been identified. The fact that these ISD are separate from the fusogenic domains of the Env proteins has allowed fully functional Env proteins with enhanced immunogenicity to be designed. This important result of the RETRO-ENDO team has been applied to the establishment of a veterinary vaccine against the Feline Leukemia Virus (FeLV).

The research activity in molecular retrovirology has been slightly more modest in the last 5 years, as the research entity moved to other research themes, however RETRO-ENDO made an important contribution in the retrovirolgy field by reporting in 2011 the identification of Ephrin A as a receptor of the IAP-E murine ERV.

A cellular electron microscopy group formed of 3 members has joined the team in 2010. Although the RETRO-ENDO research entity and the electron microscopy team had a long-lasting and fruitful collaboration for many years, the arrival of the microscopists on site will in the future certainly contribute to new synergies and strengthen the unit projects in basic retrovirology and in placenta structure. Moreover, the microcopy project aiming at deciphering the organization of paraspeckles (nuclear bodies involved in mRNA regulation) will be continued, enlarging the investigations to retrovirogy-infected cells. Thus, the arrival of the electron microscopy group in the research entity will certainly be a strong benefit for both teams.

The very creative and innovative research of the RETRO-ENDO team is demonstrated by an outstanding record of publications during the last 5 years including 5 PNAS, 1 PLoS Pathogens, 1 PLoS Genet., 2 J. Virol., 2 Retrovirology, 1 Genome Res., 1 Mol. Ther., 1 Placenta, corresponding to studies performed in the laboratory, i.e. with a RETRO ENDO team member in first and senior author. In addition, the RETRO-ENDO team members have been associated in collaborative studies published in major international journals : Science, Cell, Nucleic Acids Res., J. Gen. Med., J. Virol., J. Clin. Virol.

Assessment of the unit's academic reputation and appeal

The research entity has a great ability to raise funds (ANR, INCA, AFM-Telethon) and has been rated “Equipe labellisée Ligue Contre le Cancer”. The director of the unit has received an international prize in 2009 for the team major contributions on ERVs.

The research entity is part of the LabEx LERMIT but the benefit of this connection and the unit’s interactions with other groups at the Gustave Roussy Institute and the university have not been presented, both in the written report and during the visit.

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

The research entity has filled many patents in the recent years (7 patents since 2005), and has excellent connections with industry through its work on vaccines. RETRO-ENDO was able to establish many industrial contracts and was at the initiative of creating a spin-off start-up company that employs a full-time scientist as well as a PhD student (allocation CIFRE). Partnership with industry was implemented by the licensing of a new vaccine against the Feline Leukemia Virus, which is sold in the USA since March 2012.

The research entity has produced many reviews in English (Biologicals, Placenta, Philos Trans R Soc Lond B Biol Sci, Current Opin Virol) and French (Médecine/Sciences, Virologie) to communicate to a wider scientific audience. The unit has made also numerous contributions to the dissemination of scientific culture to the general public in various national (Le Monde, La Recherche) or international (New York Times) media.

Assessment of the unit's organisation and life

The life of the RETRO-ENDO research entity is organized around a weekly meeting where are discussed the scientific work progresses of all unit members. This format is very suitable for PhD and post-doctoral students, whose work is very well supervised. Curiously, these meetings do not include the microscopists (perhaps because this group does not include any student), and this will certainly hamper the progressive integration of this small group in the unit research programs. Moreover the size of the electron microscopy group will even decrease this year with the retirement of an engineer who will not be replaced.

Some opportunities to explain the decisions taken by the director lack in the unit's life, especially for the technicians and engineers. This would undoubtedly stimulate discussions on aspects other than those related to science and bring a little more collegiality in the decisions.

To date, the head of the research entity is the only effective PhD student supervisor. In practice, several members of the unit who do not have their accreditation (habilitation à diriger des recherches - HDR) co-supervise PhD students with the head of the unit. However, the fact that these researchers have not yet the ability to fully and formally assume their PhD supervisor's role appears as a weakness for the unit. The unit publication record shows also that the scientists never publish as senior authors (except for one publication in co-last authorship during the last 5 years). Although the level of publication is excellent, this could represent a problem for the career of these researchers and for the emergence of a scientific leadership in the future.

Assessment of the unit's involvement in training through research

PhD students and post-doctoral students are particularly well supervised and publish all as first authors in excellent journals. Most of the former PhD students obtained a tenured position in research, including two present members of the team. Over the past 5 years, only one PhD thesis was defended in the unit, which is rather low. This will be improved in the coming years as there are currently 3 ongoing theses in the unit (including one CIFRE thesis) (Doctoral school B3MI ED N°516). A student who will obtain its PhD degree in a few months has already two publications in PNAS as first author, showing the high level of publication of the RETRO-ENDO team students and therefore the quality of their management.

The research entity is not involved in teaching programs of masters or doctoral schools, but this is probably due to the fact that all unit members are full-time researchers.

Assessment of the strategy and the five-year plan

The planned projects, described shortly in the written report and during the visit, are in continuity with the previous works. The committee identified that a potential risk could be to have too many sub-projects within the unit for human resources that remained quite stable during the last years (a full time researcher and an assistant-professor recently left the unit).

The projects aiming at the fine-tuned characterization of the cellular and molecular mechanisms of the retroviral env-mediated immunosuppression appear ambitious and very promising. The research program proposes also to investigate the potential specific involvement of their immunosuppressive activity in tumor development in humans and in feto-maternal tolerance in mammals (murine and human models). Beyond the importance of understanding these mechanisms, these studies could have important therapeutic applications, leading to the development of optimized vaccines against retroviruses, including human retroviruses (HIV, HTLV-1).

The RETRO-ENDO research entity proposes an appropriate blend of studies based on experimental knock-out in mice and in different mammal families in order to understand the role of syncytins in placental development and in the establishment of materno-fetal tolerance. In addition, the potential role of these viral-derived proteins in physiological processes (such as macrophage fusion, osteoclast formation, myoblast fusion and myotube formation) will be investigated. The RETRO-ENDO team wishes also to explore the possibility that mutations in the syncytin genes might lead to alteration of placentation and/or other pathological processes.

The research programs on basic virology will follow the recent discovery that the envelope of a human endogenous retroviruses (ERV)(HERV-K HML2) can antagonize tetherin, an inhibitor of lentiviral particle release. Future investigations in this specific domain will be to decipher the mechanisms leading to the tetherin inhibition, to search for an elusive receptor for this ERV and to examine the possible involvement of this interplay in modifying

cellular physiology. These objectives are interesting, and might provide suitable ground for further career development of a young researcher who will supervise more particularly this research area.

All the scientific questions are pertinent and the expert committee, given past performances, has a high confidence in the capability of the research entity to reach most of the aims presented.

4 • Conduct of the visit

Visit date:

Start:	Thursday, 13th February 2014 at 8:00 am
End:	Thursday, 13th February 2014 at 4:45 pm

Visit site:	"Bâtiment de recherche 2"
	Salle de Conférence Roger Monier
Institution:	Institut Gustave Roussy
Address:	114, rue Édouard-Vaillant, Villejuif

Conduct or programme of visit:

Welcome

Closed door committee membres meeting

Key achievements and project presentation by the head of the unit (presentation - discussion)

Key achievements and project presentation by the head of the cellular electron microscopy team (presentation - discussion)

Meeting with institution representatives

Meeting with the doctoral school ED 516 representative

Meeting with scientists

Meeting with technical staff

Meeting with PhDs and post-docs

Meeting with head of the team

Committee closed door meeting

5 • 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 15 avril 2014

N/Réf. : 110/14/JB/LM/AL

Objet : Rapport d'évaluation d'unité de recherche
N° S2PUR150007979

Monsieur le Directeur,

Vous m'avez transmis le 28 mars dernier, le rapport d'évaluation de l'unité de recherche « Physiologie et pathologie moléculaires des rétrovirus endogènes et infectieux » - N° S2PUR150007979, et je vous en remercie.

L'université prend bonne note de l'appréciation et des suggestions faites par le Comité.

Vous trouverez en annexe les éléments de réponse de Monsieur Thierry HEIDMANN, directeur de l'unité de recherche.

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

Pour le Président empêché
La Vice-Présidente

UNIVERSITÉ PARIS SUD
PRÉSIDENCE
Bâtiment 300
91405 ORSAY cedex

Jacques BITTOUN
Président

Colette VOISIN

Siège :
Université Paris-Sud
15 rue Georges Clemenceau
91405 Orsay cedex
www.u-psud.fr

Tél : 01 69 15 74 06 – Fax : 01 69 15 61 03 - e-mail : president@u-psud.fr

CNRS UMR 8122 Rétrovirus Endogènes et Eléments Rétroïdes des Eucaryotes Supérieurs
Institut Gustave Roussy, 114 rue Edouard Vaillant, 94805 Villejuif, France
Thierry HEIDMANN

Observations de portée générale

1- Contrairement à ce que pourrait laisser craindre le présent rapport, le groupe de G. Pierron est parfaitement intégré au sein de l'UMR. Tout d'abord, une collaboration a été établie de longue date avec ce groupe, bien avant leur arrivée dans l'Unité, sur des bases scientifiques solides et réelles ayant d'ailleurs conduit à la publication de toute une série d'articles de très bon niveau. Ce groupe travaillait précédemment à l'Institut André Lwoff à Villejuif, et nous avions déjà à l'époque des réunions fréquentes, facilitées par la proximité des lieux. L'arrivée du groupe de Gérard Pierron en février 2011, que j'ai vivement souhaitée et que l'IGR a très fortement soutenue, n'a fait que renforcer cette collaboration. Même si le microscope électronique est situé au rdc pour des raisons techniques, le bureau de G Pierron est situé à notre étage (bureau commun avec Anne Dupressoir, pièce de labo Biol Mol également à l'étage) et les interactions sont directes, quotidiennes et fructueuses. Comme il l'a rappelé dans son exposé, G Pierron poursuit en effet avec nous une recherche sur l'ultrastructure des ERVs et les structures placentaires, encore une fois avec des publications communes, et réciproquement les modèles animaux sur lesquels nous travaillons lui ont permis de trouver des modèles de choix (e.g. le placenta d'opossum) pour les études qu'il mène sur les paraspeckles.

2- Concernant la communication au sein de l'Unité, en particulier avec le personnel ITA, je voudrais rappeler que ceux-ci participent au même titre que les chercheurs (stagiaires, doctorants, post-doctorants, statutaires) aux réunions de laboratoire hebdomadaires, qui intègrent la discussion des sujets scientifiques et des sujets plus administratifs.

3- Concernant le nombre de personnel HDR, ils sont depuis plusieurs années au nombre de 3, et Anne Dupressoir (CR1 INSERM), qui a supervisé effectivement des stagiaires M2 et maintenant des étudiants en Thèse, vient d'obtenir son HDR (le 4 Mars 2014, soit 3 semaines après la visite du Comité, comme nous l'avions indiqué). La prochaine chercheuse susceptible de postuler à l'HDR est Marie Dewannieux (CR1 INSERM), qui actuellement supervise une première Thèse et devrait sans aucun doute pouvoir postuler à cette qualification d'ici un an ou deux. Ces deux chercheuses ont par ailleurs publié et/ou soumis récemment des articles où elles sont dernières ou co-dernières signataires.

4- Concernant l'isolement au sein de l'IGR, nous avons mentionné les collaborations du Groupe de G Pierron avec de nombreuses Unités des Bâtiments de Recherche (plusieurs Unités CNRS et INSERM),

parmi lesquelles on peut citer celles de Guido Kroemer (plus de 20 publications communes), d'Eric Solary et Olivier Bernard, ou de Joelle Wiels. Par ailleurs, les chercheurs de notre Unité interagissent directement avec ceux des autres Unités, et ces interactions sont favorisées par l'existence au sein des Bâtiments de Recherche de plate-formes très bien structurées (Protéomique, Génomique, Imagerie, Bioinformatique, Centre de Ressources Biologiques) avec lesquelles nous avons de nombreux programmes en cours et qui constituent autant de «nœuds de communication» et de liens entre les chercheurs et techniciens du Bâtiment.

Bien cordialement,

Thierry Heidmann
Directeur de Recherche CNRS
Directeur de l'UMR8122
Institut Gustave Roussy
94805 Villejuif
heidmann@igr.fr