Approches génétique intégrées et nouvelles thérapies pour les maladies rares

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Integrated genetic approaches in therapeutic discovery for rare diseases

Integrare

Under the supervision of the following institutions and research bodies:

Université d'Evry-Val-d'Essonne - UEVE

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

École Pratique des Hautes Études - EPHE

Généthon

December 2013

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. Hans YSSEL, 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:	Integrated genetic approaches in therapeutic discovery for rare diseases
Unit acronym:	Integrare
Label requested:	
Present no.:	UMR 951
Name of Director (2013-2014):	Ms Anne GALY
Name of Project Leader (2015-2019):	Ms Anne GALY

Expert committee members

Chair: Mr Hans YSSEL, CIMI, Paris

Experts:

Mr Toni CATHOMEN, University of Freiburg, Germany

Ms Bénédicte CHAZAUD, Institut Cochin, Paris

Mr Joël DREVET, Inserm Clermont-Ferrand (representative of the CNU)

Mr Stefan KARLSSON, Lund University, Sweden

Mr Christian MUCHARDT, Institut Pasteur, Paris

Ms Els VERHOEYEN, École Nationale Supérieure Lyon (representative of CSS Inserm)

Scientific delegate representing the AERES:

Mr Joost VAN MEERWIJK

Representatives of the unit's supervising institutions and bodies:

Mr Patrick CURMI, Université d'Evry-Val-d'Essonne

Ms Florence GONNET (representative of Doctoral School n°423)

Mr Jean-François JEANNIN, École Pratique des Hautes Études

Mr Franck LETHIMONNIER, Institut National de la Santé Et de la Recherche Médicale

Mr Andras PALDI (representative of Doctoral School n°472)

Mr Frédéric REVAH, Généthon

1 • Introduction

History and geographical location of the unit

The current UMR-S951 (Molecular Immunology and Innovative Biotherapies, 2009-2013) is structured as a single unit (team 1), representing one of the research groups of the R&D department at Genethon, with three main axes of research:

(I) elaborate treatment of primary immune deficiencies by gene therapy with the use of advanced vectors;

(II) study mechanisms of vector/cell interactions, in particular those that cause epigenetic changes in transduced cells;

(III) study immune responses induced by viral vectors in vivo.

The unit has grown from 18 staff members to 28 in 2013, 21 permanent staff and of these 12 permanent research staff, two postdocs and four PhD students.

The new UMR proposes an extensive translational research program, involving biological systems and pathophysiology, genetics and gene-based technology with the perspective to develop novel therapies for rare genetic diseases. Because of significant interactions that have been established during the past five years between researchers of team 1 and the incoming team 2 (Novel gene-based therapies for neuromuscular diseases: Mr Fulvio MALVILIO), both teams will be associated within a single unit for the purpose of further enhancing interactions and building future synergies. Each team will have several groups of researchers with specific projects.

The new UMR, tutored by Inserm, UEVE, EPHE and Genethon, will form the "Academic Research" group at Genethon and will be located at Genethon, 1bis Rue de l'Internationale - 91000 EVRY.

The team joining this new UMR is currently at Genethon.

Management team

The new UMR will be headed by Dr. Anne GALY who also heads team 1. She will be assisted by Dr Fulvio MALVILIO (Chief Scientific Officer of Genethon and head of team 2).

AERES nomenclature

SVE1 LS7 (biomedical technology)

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	7	7
N2: Permanent researchers from Institutions and similar positions	4	6
N3: Other permanent staff (without research duties)	10	14
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	2	7
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**24**	**34**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit*	1	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	5	6

2 • Overall assessment of the unit

The director of UMR-S951 has high international visibility, strong international collaborations and is lead-partner in international networks.

UMR-S951 has carried out successful preclinical research resulting in four international clinical trials and has been instrumental in drawing full benefit from original methods that have been developed, including patent filing. There is an active partnership with patients' groups. Although acting as a dynamic interface between academia and biotechnology industry, the level of academic output of the unit is average and is perfectible.

The UMR is characterized by a very good internal organization permitting the establishment of optimal interactions between all groups. Free core facilities at Genethon allow for very good accessibility to research platforms.

The UMR is well implicated in university teaching, makes strong efforts in training doctoral students and is strongly involved in the training programs of the Doctoral Schools of Université d'Evry and the EPHE.

UMR-S951 has developed an exciting five-year plan with high-risk elements. The strategy is based on excellent cell biology and translation of experimental results into clinical applications. There is, however, a need for some refocusing. Combining the future teams to form a new research unit will increase critical mass. Synergistic, mutually beneficial, interactions between these teams will permit the achievement of proposed projects.

Strengths and opportunities related to the context

- **Strengths**

The unit has strong international visibility and recognized expertise in the field of gene therapy, in particular in Wiskott Aldrich Syndrome gene therapy with gene-corrected stem cells, using lentiviral hematopoietic gene therapy, and more recent expertise in X-linked chronic granulomatous disease with engraftment of gene-modified hematopoietic stem cell and granulocyte correction.

The director is lead-partner in several international networks: ongoing international clinical trials and collaborations with groups in London, Boston, Milano, and Paris, as well as an EC network with eleven other European laboratories.

Genethon provides very good access to various core facilities.

Strong collaboration with Genethon allows for excellent valorisation of research towards clinical applications.

This Unit constitutes a dynamic interface between academia and biotechnology industry.

Quality of the SWOT analysis is excellent, realistic and self-critical.

- **Opportunities**

There is ample opportunity to associate with other researchers at Genethon thus increasing critical mass. Establishment of team 2 will strengthen the UMR and generate an even stronger team in neuromuscular disorders.

Genethon is in a favorable phase for the development of excellence in academic activity and research.

There will be the opening of an academic environment close to Genethon with the establishment of a large campus at the Université Paris Saclay.

Weaknesses and threats related to the context

Scientific output in terms of publications (impact factors) is average.

Research focus is wide rather than deep.

The current UMR has suboptimal critical mass and an imbalance between the number of investigators/Staff Scientists and Postdocs/PhD students.

The unit faces the challenge to maintain an adequate balance between academic and applied activities.

The UMR lacks sufficient expertise in bioinformatics.

A complex organization makes it a challenge to direct a unit where several independent organizations are involved to support and finance the operation.

The UMR is physically separated from a strong University Hospital as well as a strong academic environment, which is definitively a weakness and possibly a threat for development of original research beyond state-of-the-art.

Strong competition in the field.

Recommendations

The project on increasing efficiency of lentiviral transduction focuses on viral entry, but does not fully take into consideration the cell biology aspects of stem cells to improve their survival, activation, maintenance or possible increase in self-renewal to improve gene transfer efficiency. The focus on cell biology should be improved instead of only focusing on the vector/viral issues. The director has a strong background in cell biology from her years as an immunologist and could contribute.

There are many projects within the UMR that are somewhat disperse. The question is whether all these projects can be internationally competitive at the highest level. The program should be focused more to generate international competitiveness. The most important projects are the immunodeficiency projects and improvement of lentiviral gene transfer. The immune response to viral DNA seems out of focus of the main program and it is unclear whether the immune sanctuaries and epigenetics part can be competitive.

The unit has many permanent employees and relatively few postdocs and PhD students. It may lead to a more dynamic, original and creative environment if a higher number of outstanding postdocs with transient employment of 3-4 years come to generate innovation and leave once their project is finished.

3 • Detailed assessments

Assessment of scientific quality and outputs

The UMR has a high-risk approach with methodological breakthroughs. There is an excellent focus of UMR 951 on translational research and the development of novel tools to achieve safe and efficient gene therapy in primary immune deficiencies. In particular, its preclinical research on Wiskott Aldrich Syndrome (WAS) has explored an original approach. Experimental data obtained from models of WAS gene therapy and lentiviral technology have been successfully translated into ongoing international Phase I/II clinical trials of gene therapy for WAS in France, Great Britain and the United States. The development of strategies of lentiviral-based gene therapy by the unit is highly promising, as WAS lentiviral vectors - unlike LTR-driven Murine leukemia viral vectors, the use of which has led to a high frequency of leukaemia – do not have transforming activity. At present, seven patients have been treated using the lentiviral-based gene therapy developed at Genethon with encouraging results. Results from a parallel trial involving treatment of three WERE patients with TIGET in Milano, Italy, with the same vector have been published recently with the UMR's director as collaborator in this study. Results from these studies have been published. More recently, expertise in the clinical grade manufacturing of a lentiviral vector to be used for the treatment of X-linked chronic granulomatous disease has been acknowledged, as part of an EC network with 10 others European laboratories. However, no results have been published as yet.

Mechanisms that induce humoral immune-responses against viral components of recombinant adeno-associated viral vectors (rAVV) have been investigated using various murine models with targeted mutations in genes involved in innate immune responses. This work has been published.

The UMR has developed a family of cationic amphipathic peptides referred to as Vectofusins® that are active on several lentiviral subtypes and that enhance the frequency of transduced hematopoietic stem cells. One of these peptides in particular, Vectofusin-1®, a promising additive that could significantly ameliorate hematopoietic stem cell gene therapy, has been published, trademarked, and patented.

The UMR is exploring different epigenetic contexts (histone modifications) that will affect retroviral vectors in their choice of integration sites. It has also taken up the very important issue of determining the impact of gene transfer protocols on the epigenetic status of the host cells. This has allowed them to document changes in DNA methylation induced by the cytokines used for pre-activation of the cells, but also by the lentiviral vector itself. These approaches will be very precious to design safer protocols and vectors. To increase efficiency of gene transfer, the UMR finally shows much interest for the fluctuating expression of both endogenous genes and transgenes. This project, at the interface between epigenetics, vectorology, and systems biology is carried out in collaboration with cellular biology and bioinformatics labs in the context of an ANR-program.

The immunology project, involving immune sanctuaries in the field of neuroimmunology has yielded no publications yet within the setting of the UMR-S951

During the period 2008-2013, 46 original peer-reviewed articles with one team member as first and/or last co-author have been published. Although the very good experimental results have been published in solid specialized scientific journals (Gene Ther, Mol Ther, PloS One, Hematologica and Mol Ther Nucleic Acids), output in terms of impact factor needs to be improved.

The experts committee judges the cited scientific output "very good".

Assessment of the unit's academic reputation and appeal

Members of the unit have been part of organizing committees for national and international congresses in the field of gene therapy, gene expression, and neuroimmunology and are regularly invited to international conferences, as speakers or chairpersons, as well as invited seminars and lectures.

The UMR's director is on the editorial board of the journal Human Gene Therapy and on the Gene Therapy committee of the International Society for Cell Therapy. She participates in and coordinates international research programs and is lead partner in international networks.

Members of the UMR participate in scientific evaluation committees and the director is president of the CSS8 permanent scientific evaluation commission of the Inserm.

UMR-S951 has been highly successful in the establishment of international networks and participation in EC-FP6 (n=1) and EC-FP7 (n=3) grants resulting in high number of international collaborations. The UMR has been successful in raising funds from national, institutional, and private funds.

Based on these observations, the experts committee judges the academic reputation and appeal of the UMR "excellent".

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

An important asset of the research program of the UMR is its strong involvement in translational research with a clear aim at bringing results generated from basic research to clinical applications. Work carried out by the team has an important impact on therapeutic approaches with respect to gene transfer. Two patents, pertaining to the development of peptides with viral infection-enhancing properties and production of enveloped viruses, have been deposited.

All members of UMR-951 are actively involved in the dissemination of scientific knowledge to the general public, via organized visits to Genethon, open days for various patient's associations and AFM/Telethon events. Overall contribution of the unit to interactions with social, cultural and economic environment is estimated at close to 10% of time.

These observations indicate an "outstanding" level of the UMR's interaction with its social and economic environment.

Assessment of the unit's organisation and life

UMR-S951 has an excellent internal organization facilitating the interaction between the different groups as well as with members of team 2 who will join the new UMR. Institutional budget allocations are shared to purchase common supplies and to support interns and students if needed specifically. The UMR's director manages the funds and the budget requests following consultation with each of the partners and the team members. All team members expressed satisfaction about the organization of the UMR. There is a very good integration of the different groups in the overall project. This is furthermore facilitated by the very good access to core-facilities and research platforms at Genethon. It is to be noted, however, that the units lacks good access to /does not possess expertise in bioinformatics which hampers efforts to manage, analyze, and process biological data. The current website of Genethon does not allow for sufficient visibility of the various groups within the unit. This shortcoming should be corrected.

Based on these observations, the experts committee felt that the UMR's organization and life is "excellent".

Assessment of the unit's involvement in training through research

The UMR is affiliated with the Université d'Evry Val d'Essonne (UEVE, Doctoral School related to Biology entitled "des Génomes aux organismes"; ED423), the "École Pratique des Hautes Études" (EPHE: Doctoral School n°472), a leading institution of higher education and research, providing highly specialized training in basic and applied research, and the Doctoral School n° 273 "Biologie et biotechnologie" (B2T) of the Université Paris Diderot – Paris 7.

According to the respective representatives of both institutions, the Doctoral School of the Université d'Evry allows PhD students to be supervised by the scientists from the Inserm UMR, provided that the latter have acquired the accreditation to supervise research (HDR). This is also the case for the EPHE; however, as the EPHE is a rather small, pluridisciplinary school, there are only a limited number (five to six) PhD-scholarships for biology available each year. Moreover, the UEVE has a changing policy each year and communicates rather late in the academic year whether they allow only one or two students per PI-HDR to apply, which can lead to an organizational problem for the PIs. In spite of the efforts put in by both Doctoral Schools, the actual situation only provides a minimal number of PhD students per year, which is clearly not enough to reach a critical mass of doctoral students in the UMR.

Two main actions have been identified to try and remedy this situation that should be, or are currently being, explored: 1) Obtaining PhD salaries through competition for grants by the different PIs in the unit (e.g. an Advanced ERC grant has been obtained by team 2 allowing to hire more PhD students) and 2) As Genethon, being a private entity, cannot finance directly PhD students, to explore the possibility how this institution can augment the critical mass of PhD scholarships for the two Doctoral Schools. This was also mentioned as an action being currently explored by the president and the scientific director of Genethon. Clearly, an ambitious postdoctoral program will give the UMR much more international visibility and will lead to a more dynamic, original, and creative environment.

At present, UMR-S951 has three university professors (UEVE 2, EPHE 1), three assistant professors (UEVE 2, EPHE 1) and one Research Assistant (UEVE) who are involved in teaching in Molecular and Developmental Biology, Genetics, Epigenetics, Immunology, Cell and Gene Therapy and Biotechnology.

The UMR's director is faculty of the Translational Research Training in Haematology, a joint training program of the American and European Societies for Haematology.

The UMR has received a total of 39 interns - rotation between one and six months - for L3, L3 pro, M1 and M2 students, whereas two PhDs in the fields of molecular biology and epigenetics, respectively, were produced with four PhD students currently working in the fields of immunology and molecular biology.

Altogether, the experts committee felt the UMR has a "good" involvement in teaching through research.

Assessment of the strategy and the five-year plan

Both team leaders present an exciting five-year plan of translational research with high-risk elements. The addition of a second team to UMR-S951 brings along a strong and internationally recognized expertise in molecular biology, genetics, muscular dystrophies, and neuro-muscular disease. This extension of the original UMR will increase its critical mass and will help to develop cutting edge concepts and technologies to improve translational research, which remains the hallmark of the new UMR.

The future UMR will consist of seven adequately balanced groups (organized into two teams) of roughly equal size with satisfactory mentoring potential and excellent technical support within a high quality research environment provided by Genethon. Based on excellent results obtained by team 1 and team 2 with respect to gene-based therapies of immuno-deficiencies and (neuro)muscular disease, respectively, the strategy to profit from the synergy of both teams is an excellent choice and will ensure the further development and feasibility of the strategies and projects put forward in the project.

This regrouping will also increase the academic appeal of the new UMR; it is however important to implement a strong postdoctoral program that will not only attract highly qualified post-docs, but that will also contribute to a dynamic scientific environment.

The main core of the program of team 1 is the preclinical and clinical work that involves transduction of hematopoietic stem cells, as well as immunology studies in gene transfer settings that use DNA vectors (AAV), which represents good to excellent work. Although it might be possible to reduce this part of the project in order to focus more on the lentiviral work in hematopoietic stem cells, an advantage of continuing the immune-AAV work is the collaboration with team 2 where AAV vectors are used thereby maintaining its scientific level.

The approaches of the group working on stochastic fluctuations in gene expression are original, but the group needs a high profile publication in the area to demonstrate that it is competitive. The complementary work on the impact of gene transfer technology on host cell epigenetics must be acknowledged as very useful for the scientific community. Structurally, this group, that by its composition has much contact with the university, would benefit from a more proactive student policy.

The other immunology project, involving immune sanctuaries in the field of neuroimmunology, as well as the epigenetics studies are much less impressive than the main core of the program. team 1 is unlikely to remain competitive in the long run if it maintains its broad focus on three categories of rather dissimilar projects.

Given these observations and considerations, the experts committee judges the strategy and five-year plan "excellent".

4 • Team-by-team analysis

Team 1: Blood and immune systems: a target for treatment and host-vector interactions

Name of team leader: Ms Anne GALY

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	7	5
N2: Permanent EPST or EPIC researchers and similar positions	4	2
N3: Other permanent staff (without research duties)	10	9
N4: Other professors (PREM, ECC, etc.)	1	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**24**	**18**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	5	4

• Detailed assessments

Assessment of scientific quality and outputs

Based on a strong collaboration with Genethon, this team has developed a high-risk approach with methodological breakthroughs. There is an excellent focus on translational research, in particular the development of novel vectors to safely and efficiently deliver gene therapy to patients with primary immunodeficiencies. There is

internationally recognized expertise in Wiskott Aldrich Syndrome (WAS) hematopoietic stem cell (HSC)-corrected gene therapy using a lentiviral vector system that has been developed by this team. Experimental work carried out by the team has underscored the absence of transforming properties of the vector in immortalisation assays, in contrast to earlier MLV-based vectors that were found to induce a high frequency of occurrence of leukaemia in treated WAS patients. Indeed, as of yet, the use of this vector in several international clinical trials in collaboration with teams in Paris, London, Boston and Italy has yielded promising results showing stable engraftment of WASP-expressing cells and clinical improvement and no selection of viral integration near oncogenes. These results have been published with the team's director as co-author, in the journal Science.

More recently, expertise in X-linked chronic granulomatous disease (X-CGD) with engraftment of gene-modified HSC and granulocyte correction has been acknowledged. The group leader coordinates an EU network with eleven other European laboratories and is involved in the development of an externally generated lentiviral vector, which includes non-clinical regulatory studies and manufacturing/development of the vector to GMP standards.

It shows strength that the most outstanding groups in clinical gene therapy of inherited blood disorders are collaborating with the team and it needs to be emphasized that essential original scientific contributions are performed at Genethon that cannot be performed efficiently by the leaders of these clinical studies.

Excellent work in this team has resulted in the development a family of cationic amphipathic peptides referred to as Vectofusins® that are active on several lentiviral subtypes and that enhance the frequency of transduced hematopoietic stem cells. One of these peptides in particular, Vectofusin-1®, a promising additive that could significantly ameliorate hematopoietic stem cell gene therapy, has been published, trademarked, and patented.

The team has also worked on understanding epigenetic modifications induced by gene transfer in HSC, i.e. changes in the DNA methylation profile upon lentiviral transduction and preactivation with cytokines. This has allowed them to document changes in DNA methylation induced by the cytokines used for pre-activation of the cells, but also by the lentiviral vector itself. These approaches will be very precious to design safer protocols and vectors. To increase efficiency of gene transfer, the team finally shows much interest for the fluctuating expression of both endogenous genes and transgenes. However, this project being at the interface between epigenetics, vectorology, and systems biology requires bioinformatics, which is not in their field of expertise and is therefore carried out in collaboration with a bioinformatics lab in the context of an ANR-project.

Gene transfer in immune sanctuaries for the treatment of ocular diseases is a new development proposed by team 1 with the arrival of a newly recruited university professor in 2011. Production for this group from 2008-2013 is correct, but the periodic level/quality is perfectible. Citations are weak and international visibility low.

Based on the mentioned observations, the experts committee judges the scientific production of the team "very good".

Assessment of the team's academic reputation and appeal

Members of team 1 have been part of organizing committees for national and international congresses in the field of gene therapy, gene expression, and neuroimmunology and are regularly invited to international conferences, as speakers or chairpersons, as well as invited seminars and lectures.

The team's director is on the editorial board of the journal Human Gene Therapy and on the Gene therapy committee of the International Society for Cell Therapy. She also participates in and coordinates international research programs and is lead partner in international networks.

Members of the team participate in scientific evaluation committees and the director is president of the CSS8 permanent scientific evaluation commission of the Inserm.

Team 1 has been highly successful in the establishment of international networks and participation in EC-FP6 (n=1) and EC-FP7 (n=3) grants resulting in high number of international collaborations, as well as in fund raising via national, institutional, and private funds.

Based on these observations, the experts committee judges the academic reputation and appeal of the team "excellent".

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

An important asset of the research program of team 1 is its strong involvement in translational research with a clear aim at bringing results generated from basic research to clinical applications. Work carried out by the team has an important impact on therapeutic approaches with respect to gene transfer. Two patents, pertaining to the development of peptides with viral infection-enhancing properties and production of enveloped viruses, have been deposited.

All members of the team are actively involved in the dissemination of scientific knowledge to the general public, via organized visits to Genethon, open days for various patient's associations and AFM/Telethon events. Overall contribution of the unit to interactions with social, cultural and economic environment is estimated at close to 10 % of time.

Based on these observations, the experts committee judges the level of the team's interaction with its social and economic environment "outstanding".

Assessment of the team's organisation and life

This team has an excellent internal organization facilitating the interaction between the different groups. Institutional budget allocations are shared to purchase common supplies and to support interns and students if needed specifically. The team's director manages the funds and the budget requests following consultation with each of the partners and the team members. All members of the team expressed satisfaction about its organization. There is a very good integration of the different groups in the overall project. This is furthermore facilitated by the very good access to core-facilities and research platforms at Genethon. It is to be noted, however, that the team lacks good access to /does not possess expertise in bioinformatics which hampers efforts to manage, analyze and process biological data. The current website of Genethon does not allow for sufficient visibility of the various groups within the team. This shortcoming should be corrected.

Based on these observations, the experts committee feels that the team's organization and life is "excellent".

Assessment of the team's involvement in training through research

Team 1 is affiliated with the Université d'Evry Val d'Essonne (UEVE, Doctoral School related to Biology entitled "des Génomes aux organismes"; ED 423), the "École Pratique des Hautes Études" (EPHE: Doctoral School n°472), a leading institution of higher education and research, providing highly specialized training in basic and applied research, and the Doctoral School n° 273 "Biologie et biotechnologie (B2T) of the Université Paris Diderot – Paris 7.

According to the respective representatives of both institutions, the Doctoral School of the Université d'Evry allows PhD students to be supervised by the scientists from the Inserm team, provided that the latter have acquired the accreditation to supervise research (HDR). This is also the case for the EPHE; however, as the EPHE is a rather small, pluridisciplinary, school, there is only a limited number (five to six) of PhD scholarships for biology available each year. Moreover, the UEVE has a changing policy each year and communicates rather late in the academic year whether they allow one or two students per PI-HDR to apply, which can lead to an organizational problem for the PIs. In spite of the efforts put in by both Doctoral Schools, the actual situation only provides a minimal number of PhD students per year, which is clearly not enough to reach a critical mass of doctoral students in the team.

Two main actions have been identified to try and remedy this situation that should be, or are currently being, explored:

1) obtaining PhD salaries through competition for grants by the different PIs in the team (e.g. an Advanced ERC grant has been obtained by team 2 allowing to hire more PhD students);

2) as Genethon, being a private entity, cannot finance directly PhD students, studying how this institution can augment the critical mass of PhD scholarships for the two Doctoral Schools.

This was also mentioned as an action being currently explored by the president and the scientific director of Genethon. Clearly, an ambitious postdoctoral program will give the team much more international visibility and will lead to a more dynamic, original, and creative environment.

At present, team 1 has three university professors (UEVE 2, EPHE 1), three assistant professors (UEVE 2, EPHE 1) and one research assistant (UEVE) who are involved in teaching in Molecular and Developmental Biology, Genetics, Epigenetics, Immunology, Cell and gene therapy and Biotechnology. Teaching duties are considerable.

The team's director is faculty of the Translational Research Training in Haematology, a joint training program of the American and European Societies for Haematology.

Team 1 has received a total of 39 interns - rotation between one and six months - for L3, L3 pro, M1 and M2 students, whereas two PhDs in the fields of molecular biology and epigenetics, respectively, were trained with four PhD students currently working in the fields of immunology and molecular biology.

Altogether, the experts committee felt the team has a "good" involvement in teaching through research.

Assessment of the strategy and the five-year plan

The team presents an exciting five-year plan of translational research with high-risk elements. The main core of the program is the preclinical and clinical work that involves transduction of hematopoietic stem cells and ultimately leads to clinical benefit for patients with inherited blood disorders and which is highly successful. The second part of the program of the director's group represents immunology studies in gene transfer settings that use DNA vectors (AAV) which represents good to excellent work. It could be advised to reduce this part of the project in order to focus more on the lentiviral work in hematopoietic stem cells. On the other hand, one advantage of continuing the immune-AAV work is the possible collaboration with team 2 where AAV vectors are used.

The other immunology project, involving immune sanctuaries in the field of neuroimmunology, as well as the epigenetics studies are much less impressive as the main core of the program and this project remains insufficiently elaborated. A robust model of systemic immune tolerance (anterior-chamber associated immune deviation: ACAID) is mentioned in the achievements of the team, but the development of a robust experimental model of ACAID is proposed in the team's project. This issue needs to be clarified. Team 1 should make an effort to focus among the different projects proposed and it is not sure whether the development of this direction will be a valuable addition.

Development of the project on chromatin dynamics at the genomic integration site and its impact on the stability of transgene expression will require special attention by the team's members. The same comment is valid for the assessment of the means dedicated to and the feasibility of the project regarding the "non-invasive manipulation of the chromatin structure" to increase the efficiency of LV integration into the host genome. The approaches used to investigate stochastic fluctuations in gene expression are original, but the group needs a high profile publication in the area to demonstrate that it is competitive. The complementary work on the impact of gene transfer technology on host cell epigenetics must be acknowledged as very useful for the community. This group is small but relatively productive and with good networking. Structurally, this group, which by its composition has much contact with the university, would benefit from a more proactive student policy.

Overall, the five-year plan involves three categories of rather dissimilar projects and team 1 is unlikely to be competitive in the long run with each of these projects by continuing its broad focus.

In view of these observations and considerations, the experts committee judges the overall strategy and five-year plan "excellent".

Conclusion

- **Strengths and opportunities:**

Strengths:

- very strong translational research focus;

- leadership and high visibility in gene therapy field through international networks;

- access to various core facilities provided by Genethon.

Opportunities:

- to produce therapeutics that help patients suffering from primary immune deficiencies;

- to generate valuable synergies with team 2 in the field of bioinformatics and cell biology.

- **Weaknesses and threats:**

Weaknesses:

- scientific output in terms of publications (impact factors) is average;

- research focus wide rather than deep;

- imbalance between number of Pis / Staff Scientists and Postdocs / PhD students.

Threats:

- other vector production units (current and future);

- to lose visibility by becoming part of Genethon's R&D.

- **Recommendations:**

Use scientific standing in the field and the synergies with team 2 to deepen research focus.

Attract more PhD students and Post-docs.

Team 2: Novel gene-based therapies for neuromuscular diseases

Name of team leader: Mr Fulvio MAVILIO

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		2
N2: Permanent EPST or EPIC researchers and similar positions		4
N3: Other permanent staff (without research duties)		5
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		5
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6		**16**

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

• Detailed assessments

Assessment of scientific quality and outputs

Team 2 is a recently formed structure consisting of three groups, all being internationally renowned experts in gene therapy of neuromuscular diseases. All three PIs have obtained significant results and their research is at the forefront of innovation in terms of gene therapy.

This is demonstrated by the publications of the three PIs in more than 30 articles as first/second or last/before last author. The vast majority of the studies are published in journals with an impact factor over 5 and some publications even raised a high impact, such as Blood, J Clin Invest, Sci Transl Med, Circulation and Proc Natl Acad Sci USA. Moreover the three PIs participate in other numerous studies attested by their co-authorship, reflecting their

active level of collaborative work. Their impact in the field is also attested by the reviews the three PIs have published in top review journals such as EMBO J., Nature, Current series and Trends series.

The experts committee considers this an "excellent" scientific output.

Assessment of the unit's academic reputation and appeal

The team leader is a world-known expert in gene therapy and molecular biology and member of various international committees and organizations.

The activity of the three PIs in the animation of research is very high. They regularly participate in congresses and meetings as invited speakers and/or chairmen/women, give many seminars in laboratories and institutes in France and abroad. They serve on executive boards and have editing activities in scientific journals as well.

The funding of the research has been coming from several sources, of which several FP7 programmes, support from private foundations, and an ERC for the team-leader can be cited.

The team's head is Chief Scientific Officer of Genethon.

Based on the observations, the experts committee felt that this team has an "outstanding" academic reputation.

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

The three PIs have patented their research in five patents for the 2008-2013 period.

As part of Genethon, which is very active in this field, they participate in the promotion of translational research and applications of their research and also to science dissemination towards the society.

This team therefore has "excellent" interactions with the socio-economic environment.

Assessment of the unit's organisation and life

There is a very good internal organization facilitating interactions between the distinct groups of team 2. The team will include twelve persons, among them six permanent researchers and six permanent technical staff, which is a very good ratio. It includes two qualified research supervisors ("HDR").

Although there is no doubt that the three PIs will benefit from their close proximity and that of team 1, it is important for the three groups to put together their respective research in one main goal and develop synergistic interactions with each other.

All team members expressed satisfaction about the organization of the team.

The experts committee felt that this team's organization is "excellent".

Assessment of the unit's involvement in training through research

The team has trained eleven PhD students for the period 2009-2013. However, too few post-docs are currently working in team 2, which is likely due to the recent arrival of two of the three groups on the site of Genethon. It is of note and to be commended that the team strongly promotes technicians to graduate.

The PIs are involved in international and national training and teaching programs.

Training through research by this team is therefore "excellent".

Assessment of the strategy and the five-year plan

The three groups will develop their research in the direct line of their previous results, which are excellent and ensure the feasibility of the project. They will develop and investigate cutting edge concepts and technologies to improve gene-base therapies of neuromuscular diseases, in particular limb-girdle muscular dystrophies, sarcoglycanopathies, and myotubular myopathy. The joining of the groups of team 2 with those of team 1, within the R&D structure of Genethon, will provide the necessary critical mass permitting to optimally exploit these therapeutic

strategies for the treatment of such diseases. Results from this endeavour in both basic and applied research, as being carried out in the past, will continue to be beneficial for translational research projects of the UMR as a whole.

Based on these considerations, the experts committee judges the strategy and scientific project of this team "excellent".

Conclusion

- **Strengths and opportunities:**

Strengths:

- strong group of PIs who are scientifically very productive;

- impressive preclinical work based on solid genetics, cell biology and animal models;

- access to various core facilities provided by Genethon.

Opportunities:

- to form a highly competitive research unit that focuses on muscular dystrophies, backed and supported by Genethon;

- to generate valuable synergies with team 1 with respect to translation of experimental data into the clinic.

- **Weaknesses and threats:**

Part of the proposed research is highly risky.

The team is physically separated from a strong university Hospital.

- **Recommendations:**

PIs should rapidly connect with the academic environment, e.g. UEVE, to hire undergraduate and graduate students. They should also rapidly hire post-docs, which could be achieved in part through ERC support.

Because of long-standing experience of the three PIs to work independently, the experts committee recommends to put all efforts into building a strong unit with synergistic dynamics that will be beneficial to both teams.

To team up with a national of international gene-editing specialist, to jump-start the projects involving designer nuclease-mediated genome engineering.

Acquire bioinformatics expertise.

5 • Conduct of the visit

Visit dates:

Start: Wednesday December 18th 2013 at 8.30 am

End: Wednesday December 18th 2013 at 4.30 pm

Visit site:

Institution: Genethon Evry

Address: 1 bis rue de l'Internationale, 91000 EVRY

Conduct or programme of visit:

08.30 am	Door-closed meeting Expert committee members and AERES Scientific Delegate (DS)
09.00 am	Presentation by the head of the unit past activity and projects. Ms Anne GALY
09.30 am	Team 1 'Blood and Immune Systems a target for treatment and Host-Vector interactions' (head Ms Anne GALY)
10.15 am	Coffee break
10.45 am	Team 2 'Novel gene-based therapies for neuromuscular diseases' (head Mr Fulvio MALVILIO)
11.30 am	Three parallel meetings of the experts committee with: - PhD students and postdoctoral fellows - engineers, technicians and administrative assistants - researchers with permanent position (except the unit's director and team-chiefs)
12.15 pm	Meeting of the experts committee with representatives of the Université d'Evry, Inserm, EPHE, Genethon: - Dr. Frederic REVAH, chief executive officer, Genethon - Prof. Philippe HOUDI, president of the Université d'Evry - Prof. Patrick CURMI, vice-president of the Scientific Council of the Université d'Evry - Prof. Jean-François JEANNIN, directeur d'études EPHE, représentative of EPHE mandated by président Hubert BOST - Dr. Franck LETHIMONNIER, head of the ITMO Aviesan Technologies for Health, representative of Inserm
12.45 pm	Meeting of the experts committee with representatives of the Doctoral School of the Université d'Evry: - Prof. Florence GONNET, ED GAO UEVE - Prof. Andras PALDI, representative of the Doctoral School l'ED EPHE
01.00 pm	Lunch-buffet (posters)
02.00 pm	Closed-door meeting of the experts committee and DS with the unit's director and team chiefs, Ms Anne GALY and Mr Fulvio MALVILIO
02.30 pm	Closed-door meeting of the experts committee and DS

6 • Supervising bodie's general comments

Evry, le 18 Mars 2014

Michel GUILLARD
Administrateur Provisoire de l'Université d'Evry Val d'Essonne

4, Boulevard François Mitterrand
91025 Evry Cedex

à :

Didier HOUSSIN
Président
Agence d'Evaluation de la Recherche et de l'Enseignement Supérieur
20 rue Vivienne - 75002 PARIS

Réf. AERES : S2PUR150007905

Direction de la Recherche, de la Valorisation et du Transfert

Objet : Réponse au rapport du comité de visite du laboratoire INTEGRARE – UMRS 951

Monsieur le Président,

Nous avons pris connaissance avec le plus grand intérêt de votre rapport concernant le projet « Approches génétique intégrées et nouvelles thérapies pour les maladies rares » porté par Mme Anne GALY. Nous tenons à remercier l'AERES et le comité pour l'efficacité et la qualité du travail d'analyse qui a été conduit.

Ce rapport a été transmis au directeur du laboratoire qui nous a fait part en retour de ses commentaires que vous trouverez ci-joint.

Nous espérons que ces informations vous permettront de bien finaliser l'évaluation du laboratoire.

Restant à votre disposition pour de plus amples informations, je vous prie de croire, Monsieur le Président, à l'expression de mes salutations respectueuses.

M. Michel GUILLARD
Administrateur Provisoire
de l'Université d'Evry Val d'Essonne

Michel GUILLARD

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Unité Mixte de Recherche U951, Généthon, Inserm, UEVE, EPHE
« Immunologie Moléculaire et Biothérapies Innovantes »
Direction Anne Galy PhD, galy@genethon.fr

Evry, 12 Mars 2014

Anne GALY
Directrice de l'unité Inserm U951 Généthon, Inserm, UEVE, EPHE
+33 1 69 47 29 93
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Objet : **S2PUR150007905 – Observations générales**
Approches génétique intégrées et nouvelles thérapies pour les maladies rares - Integrare
E2015-EV-0911975C-S2PUR150007905-005045-RT.pdf

A la lecture du rapport d'évaluation de notre structure par l'Aeres, nous souhaitons tout d'abord remercier le comité d'évaluation pour la qualité de son analyse et pour la clarté de son rapport.

Nous sommes heureux d'avoir été évalués « excellent » ou « remarquable » sur les aspects de visibilité scientifique, d'attractivité, d'organisation, sur nos interactions avec l'environnement ou sur notre projet futur.

La production scientifique de l'équipe 1 a été jugée un peu en deçà, mais toutefois très bonne. Effectivement, dans un contexte de recherche translationnelle, la réalisation d'études précliniques ne favorise pas les publications dans des journaux généralistes de haut impact facteur. La réalisation de brevets, notamment par le Pr. Fisson, est aussi à mettre en perspective avec la qualité de la production scientifique. L'équipe 1 a toutefois publié des travaux scientifiques compétitifs sur les cellules satellites musculaires en « back-to-back » et éditorialisés, avec 3 autres groupes dans la même issue de «Development » un journal dans le top tier. Ces travaux n'ont pas été mis en avant lors de la visite du comité par souci de clarté mais s'inscrivent bien dans les intérets de l'équipe 1 pour comprendre la biologie des cellules souches somatiques adultes. L'équipe a également réalisé des collaborations qui ont été publiées dans des journaux de fort ou très fort impact.

L'évaluation de la formation par la recherche est jugée « bonne », mais nous tenons à apporter quelques éléments susceptibles d'améliorer cette appréciation. Rappelons que les enseignants chercheurs de l'équipe 1 assurent une forte charge d'enseignement, ce qui a bien été constaté par le comité. Il faut aussi donner crédit aux responsabilités administratives académiques. Le Pr. Fisson est le directeur du département de biologie de l'université d'Evry, et à ce titre coordonne les activités d'enseignement de 43 personnes (professeurs, maitres de conférences, contractuels, ingénieurs et techniciens) à l'Université. Il a initié et organise à Evry depuis 2012 un congrès annuel "Evry Bio" avec communications orales et posters, permettant des rencontres entre étudiants, académiques et industriels. L'appréciation du comité semble se baser surtout sur le faible nombre de doctorants mais ce point doit être commenté. Bien que seulement 2 doctorants apparaissent dans les tableaux « résultats au 30 Juin 2013 », 2 autres théses ont été soutenues

depuis cette date, et 2 nouvelles théses sont actuellement en cours dans l'équipe. Par ailleurs, nous souhaitons mentionner l'encadrement de 5 thèses supplémentaires qui ont été co-dirigées par les Pr. Fisson et Pr. Paldi durant la période d'évaluation (*). Ces activités n'avaient pas été mentionnées dans la section des doctorants du dossier, car elles ont été réalisées en dehors du laboratoire. Toutefois ces co-encadrements font bien partie des activités professorales et ont donné lieu à des publications communes qui ont bien été comptabilisées. Nous pensons donc que le bilan d'enseignement serait plutôt « très bon » que « bon ».

En espérant que ces commentaires pourront contribuer à renforcer notre évaluation, nous n'avons pas d'autres remarques sur le rapport qui est par ailleurs très objectif et remercions le comité de ses commentaires et suggestions pertinentes.

Avec nos respectueuses salutations,

Anne Galy, DR1 Inserm
Directrice UMR_S951

(*) Shoaib AL ZADJALI : PhD defended in November 2011 ; Co-directed by Andras Paldi
Claire GALAND : PhD defended in November 2011 ; Co-directed by Sylvain Fisson
Anim PATHARE : PhD defended in October 2012 ; Co-directed by Andras Paldi
Rym BEN ABDELWAHED : PhD defended in September 2013 ; Co-directed by Sylvain Fisson
Jérémie COSETTE : PhD defended planed in June 2014 ; Co-directed by Sylvain Fisson