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

Department for the evaluation of research units

AERES report on research units

Institute for stem cell therapy and exploration of monogenic diseases

I-Stem

Under the supervision of the following institutions and research bodies:

Université d'Évry-Val-d'Essonne - UEVE

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

January 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. Ludovic VALLIER, 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:	Institute for stem cell therapy and exploration of monogenic diseases
Unit acronym:	I-STEM
Label requested:	UMR_S
Present no.:	UMR_S 861
Name of Director (2013-2014):	Mr Marc PESCHANSKI
Name of Project Leader (2015-2019):	Ms Cécile MARTINAT

Expert committee members

Chair:	Mr Ludovic VALLIER, Cambridge University, UK
Experts:	Mr Stéphane COMMANS, Pierre et Marie Curie University
	Mr Tilo KUNATH, Edinburgh University, UK
	Ms Majlinda LAKO, Newcastle University, UK
	Mr Thomas LAMONERIE, Nice University (representative of the CNU)
	Mr Pierre LAYROLLE, Nantes University (representative of the INSERM CSS)
	Mr Francois MOREAU-GAUDRY, Bordeaux University

Scientific delegate representing the AERES:

Mr Christian DANI

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

Mr Patrick CURMI, Evry University

Ms Marie-Josephe LEROY-ZAMIA, INSERM

Mr Bernard PRUM (Doctoral School n°423 representative)

1 • Introduction

History and geographical location of the unit

The unit was created in 2005 and is part of joint venture between the Association Française contre les Myopathies (AFM) and Institut National de la Santé Et de la recherché Médicale (INSERM).

ISTEM is located in the Evry area near the Genethon.

Management team

Ms Cecile MARTINAT is the new head of I-STEM and follows Mr Marc PESCHANSKI at this post.

AERES nomenclature:

SVE1_LS4

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	2	2
N2: Permanent researchers from Institutions and similar positions	9	9
N3: Other permanent staff (without research duties)		
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	26	34
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**37**	**45**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	6	6
Theses defended	14	5
Postdoctoral students having spent at least 12 months in the unit*	5	6
Number of Research Supervisor Qualifications (HDR) taken	5	8
Qualified research supervisors (with an HDR) or similar positions	6	8

2 • Assessment of the unit

Strengths and opportunities related to the context

I-STEM has acquired a unique expertise on human pluripotent stem cells (hPSCs) and their clinical applications. The strategy to develop in parallel cell-based therapy approaches for a diversity of disease such as Huntington's disease and skin ulcer and also drug-screening projects on rare diseases is unique at the international level. This strategy is obviously ambitious but the track record of each principal investigator is reassuring and the expert committee thinks that they will deliver successful projects. Importantly, basic studies on diseases mechanisms are also a major interest and will guarantee the long-term sustainability of this unit. Overall, I-STEM is a unique structure developing translational projects competitive at the highest level and this unit represents a driving force for the stem cell field in France and abroad.

Weaknesses and threats related to the context

One issue could be a certain lack of focus. Indeed, the unit is targeting a broad number of diseases with a diversity of approaches (cell-based therapy and drug screening). Therefore, it could be challenging to be successful in everything single area. Similarly, the balance between basic studies and pure translational projects could be difficult to maintain which might ultimately decrease the capacity of this group to be innovative.

I-STEM's visibility at the international level remains limited despite impressive achievements and this could be problematic for future developments that require international collaborations.

I-STEM should be more ambitious and more systematic concerning genome editing and genome wide analyses.

These technologies represent important tools and I-STEM will need to invest resources in this area to remain competitive at the highest level.

Recommendations

The recruitment of international post-docs / group leaders will help to increase the international recognition of I-STEM. In addition, it could bring a different vision to specific projects.

Training of scientists clinicians should be a priority for the unit. Integration of PhD students with a clinical background could be very useful to develop the stem cells applications in the clinics.

The international visibility could be increased. The work generated by I-STEM is remarkable and will benefit from more exposure at an international level.

3 • Detailed assessments

Assessment of scientific quality and outputs

I-STEM has an impressive track record in the stem cell field. Each team has published in high impact journals (Nature Biotechnology; Cell Stem Cell; Lancet; J Clin Invest.) and has shown a high level of creativity. Furthermore, translational projects such as the clinical trial for the metformin represent a major achievement. Few institutes in the world have the capacity and expertise to achieve such projects.

The knowledge and the expertise on translational work and disease modelling are also impressive especially on such a diversity of diseases. Once again, very few institutes are able to manage so many projects successfully.

Publication track record is excellent especially considering the translational focus of the institute. Each team has published in high impact journals.

Importantly, basic studies of diseases mechanisms remain a major focus. Accordingly, several teams have published studies describing novel mechanisms of diseases. This aspect is essential and will continue to bring important publications.

Assessment of the unit's academic reputation and appeal

I-STEM is involved in a diversity of European consortia and is having a leading role in several projects. The reputation of I-STEM is excellent and well recognized.

Mr Marc PESCHANSKI is a worldwide recognized expert and a leader of the stem cell field who is regularly invited to speak in the most important international meetings. He is also involved in several major international initiatives in which he has an active role concerning translational aspects of hPSCs. The other group leaders are more junior and thus are less visible at the international level. Nevertheless, their reputation is growing as shown by their invitation to International meetings and to write reviews in specialized journals. So, there is no doubt that their impact will continue to grow and that they will become international leaders of their respective field.

I-STEM has achieved major objectives especially for drug discovery and cell-based therapy. However, these accomplishments could be more publicized. Indeed, few groups are aware of the projects currently developed by the unit. The metformin clinical trial and the cell based therapy project on skin ulcer are major achievements and should be promoted at the international level. Managing patients' expectation is a challenge, but should not block the unit to interact with other groups.

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

I-STEM is strongly associated with AFM and thus has regular contacts with patient associations. It is involved in the Telethon and other fund raising activities.

The unit has also developed networks of collaborations with diverse hospitals and clinicians. This aspect is essential to achieve the translational objectives of the unit.

Several group leaders are involved in EU consortia, which provide an important network of collaborators while providing the opportunity for I-STEM to share its unique expertise.

Contacts with industry represent a major activity. Several projects have developed in close collaboration with pharmaceutical companies. Furthermore, I-STEM has created a spin-off company, which will have a major role in the commercialization of the intellectual property generated by the unit. Indeed, this unit has generated 5 patents.

I-STEM has an essential role locally and at the international level. It provides training regarding hPSCs derivation and differentiation. It also co-develops project with external partners (academic / industrial).

Furthermore, the infrastructure and resources available to each group are unique in size and quality. Thus, I-STEM has an important leadership in France.

Assessment of the unit's organization and life

The governance of the unit is well established and functions well despite the complexity added by the close interaction with CECS (Centre d'Etude pour les Cellules Souches) under AFM leadership.

The organization of the unit is coherent and democratic. The group leaders meet every week and take decisions collectively. Nevertheless, there is a new leadership and the transition between Ms Cécile MARTINAT and Mr Marc PESCHANSKI is working well. Mr Marc PESCHANSKI will maintain his involvement by providing mentorship to Ms Cécile MARTINAT as the new head of unit. This interaction is very reassuring given his wealth of experience and will ensure the long-term vision for the unit.

The rest of I-STEM is also involved in the decision-making process through weekly lab meetings, presentations and journal club. Feedback to management are generally well received and result in improvements. Strategic decisions are well explained and the overall objectives of the unit is known and understood by all personnel.

Distribution of resources and funding is centrally managed through a collegial system where each group leader can propose new ideas/projects.

International seminar speakers could bring added benefit to the unit, which will benefit to be more open to external interactions. Recruitment of foreign post-doctoral fellows and group leaders would also be helpful.

Assessment of the unit's involvement in training through research

I-STEM has a high number of PhD students most of which are registered at Evry University. The corresponding doctoral school is currently being re-organized with Saclay University. There are 12 PhD students for 8 HDR. The ratio is low compared to other units, but normal for groups mainly focusing on applied research. Regional support also provides additional PhD positions.

Evry University supports only a few lecturers and thus the impact of I-STEM on teaching remains limited. However, the unit has access to a diversity of grants, sabbatical for lecturers/readers. Importantly, recruitment of new lecturers/readers has been suspended for the coming year and thus the situation is unlikely to change significantly in the near future.

Importantly, there is no faculty of medicine and no CHU in Evry. Local hospitals can accommodate medical students.

PhD students are generally successful. The average time for PhD is 42 months. PhD often results in several publications. Most of the students find a job very quickly after their PhD. 15 have a job. 9 in companies and 6 in post-doctoral positions. Overall, I-STEM seems to provide very good training to PhD students.

Assessment of the strategy and the five-year plan

The strategic plan for the next five years is a continuation of the work achieved by the unit in the past five years. The focus will remain to develop new therapies for rare diseases and to better understand their pathophysiology using hPSCs.

There is no plan to develop new tools but to build on existing resources and knowledge. For example, there is no major plan to develop new methods of differentiation, but rather to take full advantage of the existing methods. So, the major focus will remain on neuronal/ectodermal cell types.

There is no plan to develop entirely novel projects on cell based therapy or target new major diseases for drug screening. The objective is to achieve the current programs especially the most recent one while remaining open to new opportunities. New programs could be developed if basic studies lead to important discoveries for translational work.

hiPSCs are taking a predominant role in disease modelling/drug screening projects and hESCs, especially derived from pre-implantation genetic diagnosis (PGD) embryos, will become less important. Nevertheless, hESCs will remain the priority for cell-based therapy.

Several key challenges have been identified with the program around drug-screening especially small molecules optimization. Acquiring the necessary expertise is not envisaged. However, the creation of the new team focusing on stem cell platform for pharmacology is aiming to address this issue. Drug combinations and drug repurposing are two key aspects while open access to drug-screening results could also help to disseminate important information.

I-STEM is also starting to integrate new tools including genome wide analyses using Next Generation Sequencing (NGS) and genomic editing using CRIPSR technology. Both approaches could deserve a more ambitious vision.

4 • Team-by-team analysis

Team 1 : Neurodegenerative/Retinal diseases

Name of team leader: Mr Anselme PERRIER

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
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.)	8	11
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**11**	**14**

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

• Detailed assessments

Assessment of scientific quality and outputs

Team 1 focuses on monogenetic forms of Huntington Diseases (HD) and retinal diseases (RP). This group utilizes hPSCs to better understand mechanisms of diseases and to develop novel therapies. The program is divided in three major areas cell therapy for RP and HD, disease modeling and quality control of genome and transcriptome.

The track record of this group is impressive. The team leader published regularly in high impact journals (Stem Cells 2013, J Clin Invest. 2012, Proc Natl Acad Sci U S A. 2008, Nature Biotechnology 2008) and is a well recognised expert in the neuroscience field.

This group has developed numerous protocols of differentiation, which enable the production of telencephalic neurons ($FoxG1^+$ cells) and then striated neurons cells Lateral Ganglionic Eminences (LGE). These protocols are well accepted in the field. They enable the production of functional cells and thus represent a significant advance. This work is recognized at the international level.

The Retinal Pigmented Epithelial (RPE) cell differentiation protocol is more recent and thus less validated. However, significant progresses have been made in a short period of time and in a very competitive environment. The focus on scaffold also represents a strong competitive advantage.

The work on animal models and the development of selection gene to make cell therapy safer represents an innovative work even if the application of such approach in the clinical might be challenging.

The program aiming to model HD in vitro is well advanced and has already resulted in major discovery including new genes, which could be involved in the disease onset. The disease modeling will be associated with drug screening programs, which aim to develop more phenotypic assays, molecular assays, and phenotype and molecular screenings, to validate drugs or gene therapy in vitro. This part of the program is ambitious but this team has all the expertise and skill to be successful.

Disease modeling of RP is less advanced but the focus on monogenetic form separates this program from competitors.

The new program focusing on Genome and transcriptome integrity does not really fit with the general strategy of this group. This team might struggle to have an impact without additional support and strategic directions. However, the aim of this project is commendable. Indeed, accumulation of genomic anomalies in hPSCs and differentiated derivatives represent a major challenge. A broader strategy regarding Genome wide analyses would be useful.

Assessment of the unit's academic reputation and appeal

The work generated by this group is well recognized worldwide as confirmed by around 16 invitations to international meetings. He has been involved in organizations of 3 international meetings.

This team is involved in several important EU consortia (FP6 and FP7). This aspect clearly demonstrates the importance of the work generated by this group at the international level. He got 2 ANR grants.

The team leader is recognized as a top expert in the HD and stem cell fields. Accordingly, he has published regularly in high impact journals.

The team brings together to different components of I-STEM including cell based therapy, drug screening and now next generation sequencing (NGS).

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

Team leader and colleagues are strongly engaged with patients' organizations.

The group has generated 7 reviews for experts but also for general public.

Translational work is significant. Several contacts with industry have been developed and one patent has been filed.

Assessment of the unit's organization and life

Team 1 is subdivided in 3 programs (HD, RP and NGS). This scope of these different programs is broad and might be difficult to coordinate. The coordination of this activity remains unclear and the development of each program could be better achieved independently. The program on RP represents a team by itself and could benefit from more independence.

Nevertheless, the general organisation of the team follows conventional rules and seems to work well.

Assessment of the unit's involvement in training through research

The team hosts PhD students who seem to be well supervised. Their knowledge is well established and their technical training adequate.

Previous PhD students have been successful in securing post-doctoral positions and have generally found a job rapidly at the end of their thesis.

The team takes part of the general organization of I-STEM and joins the regular meetings.

Assessment of the strategy and the five-year plan

The three main research programs are 1) Cell therapy programs for HD and RP; 2) Disease modeling and drug screening for HD; 3) To develop next generation sequencing (NGS) applications for addressing questions raised by programs 1) and 2).

The five years plan for the HD subgroup is ambitious but achievable. The focus on HD is important and will generate interesting data. Cell based therapy could be a major development. However, the basic studies need to be supported since they will enable the development of better strategies for drug screening.

Developing cell based therapy and drug screening approaches for RP in parallel could be challenging. The program on RP is likely to be the most difficult to fully achieve. The competition is important and innovative strategy might be difficult to develop. The interactions with international consortia will be essential.

The program around NGS is essential since this tool will be necessary to quality control cells but also for studying molecular mechanisms of diseases. So, this part could be reinforced to enable broader number of applications. In house bio-informatics support could become necessary. Further expertise on RNA-Seq/ChIP-Seq could help to initiate new projects. Thus, a broader vision including epigenetic analyses could be essential for this new program.

Conclusion

Team 1 is a strong research group, which has been successful and is an important leader in the field. This team has demonstrated its capacity to secure funding with national and international grants. This is also a productive lab with a solid track record (n=11) and several interactions with industry. The committee was very supportive and found this group to be recommended at the excellent level.

- ***Strengths and opportunities:***

The expertise of the team and its international visibility.

- ***Weaknesses and threats:***

The relative complexity of the team might limit the impact of some studies.

- ***Recommendations:***

The subdivision in three sub groups might not be optimal. There is not obvious linked between HD, RPE and NGS program. The RP sub team could become independent and could be better placed in an environment with strong focus on eye disease such the Institut de la Vision. The strategy around NGS needs to be reinforced and clearly defined. The absence of in house bio-informatics support is a concern.

Team 2 : Neuromuscular diseases

Name of team leader: Ms Cécile MARTINAT

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
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.)	6	8
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**8**	**10**

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

• Detailed assessments

Assessment of scientific quality and outputs

Team 2 has worked the past 5 years on Myotonic Dystrophy type I (DM1) using PGD-derived hESCs. The team 2 has used protocols to differentiate these cells into different cell types affected by the diseases including Mesenchymal Stem Cells (MSCs) and NPCs. Using this approach, splice defect affecting the Insulin receptor was identified. Furthermore, whole genome analyses have identified additional genes possibly involved in the disease. This work was combined with drug screening which uncovered that metformin could rescue splice defects. Based on this result a clinical trial has been initiated on 40 patients. This is a unique example where disease modeling *in vitro* had had a direct impact on clinical development. This is an impressive achievement, which validates a major part of the strategy developed by I-STEM. This project will have an important impact on the Stem cell field worldwide. Furthermore, it demonstrates that the approach developed by this team can have a direct translational impact.

More recent work includes the development of new protocols of differentiation to generate motor-neurons (MN) with different function. These protocols allow the generation of near homogenous population of different MN subtypes. This approach represents a progress when compared to previous methods, which were not efficient and only work with a limited number of cell lines. Similar efforts are currently conducted for cardiac differentiation. The next step is to apply this diversity of protocol on neuromuscular diseases including SMA. A Si-RNA screen will then be employed to find new targets provoking the disease.

Importantly the main goal of this group is to understand the basic mechanisms of disease even if drug screening remains a major focus. Cell based therapy is unlikely to have an impact for Neurodegenerative diseases. The science generated by this team is impressive and will continue to develop in the next few years.

The team leader published in high impact journals (Cell Stem Cells 2011; J Cell Sci. 2013; Human Mol Genet. 2013) as senior author and as co-author (Stem Cells 2013; Cell Reports 2012).

Assessment of the unit's academic reputation and appeal

The work generated by this group on DM1 is exceptional and the resulting clinical trial will have a broad impact.

The team has changed of leadership in 2010 when Ms Geneviève PIÉTU left I-STEM to retire upon retirement of the previous head. Thus, Ms Cécile MARTINAT is relatively junior but has already started to build her international visibility by participating to international meetings. She has also published in high impact factor journals as last author (Hum Mol Genet. 2013, Curr Gene Ther. 2013, J Cell Sci. 2013, Cell Stem Cell. 2011). So, the expert committee agrees to say that her network of collaborators and interactions with international consortia will increase in the next few years.

The focus on disease mechanisms to identify new target for drug screening is very relevant and has already been successful with metformin.

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

The team has generated one important patent, which could attract interest from industrial partners.

Team leader and colleagues are strongly engaged with patients' organizations including DM1 patients. The clinical trial is done in close collaboration within the DM1 consortium.

The group has generated publications in "Medicine et Science" for the general public and has participated to a national radio program on Bioethics.

Assessment of the unit's organization and life

Team 2 has a coherent organization with strong focus on a limited number of diseases, which is the strength of this team. The change of leadership has occurred very smoothly and the new leader has managed the transition perfectly well. This is a healthy group with a strong potential for future development.

Assessment of the unit's involvement in training through research

The team hosts 5 PhD students who are well supervised. Their knowledge is well established and their technical training is adequate. Several members of the team teach at the local university.

Previous PhD students have been successful in securing post-doctoral positions and have generally found a job rapidly at the end of their thesis.

The team takes part of the general organization of I-STEM and joins the regular meetings.

Assessment of the strategy and the five-year plan

The five years plan for this team is well organized with precise objectives around disease mechanisms. Four main research programs will be developed: Systematic high throughput assay for production of neuronal subtypes; Disease modeling and drug screening for DM1; Disease modeling and drung screening for SMA; Large-scale functional screening targeting alternate splice defects associated to DM1 and SMA. The team leader wants to apply the approach developed on DM1 on other type of neuromuscular diseases such as SMA, focusing first on the mechanisms and then on identifying new targets for drug development. These goals are ambitious but achievable. The recent development of directed protocol of differentiation to generate MN and Cardiac cells is an important achievement since it will enable further studies on a diversity of cell types. Furthermore, these protocols could be compatible with drug screening platform and enable more specific screen. Overall, this team has already acquired all the tools necessary for their future projects.

Conclusion

Team 2 is a relatively new group, which has already made an important participation in the stem cell field and has achieved major goals including the development of a clinical trial. Future projects are important and will lead to interesting results.

- ***Strengths and opportunities:***

The focus on disease mechanisms combined with drug screening.

Expertise in differentiation.

- ***Weaknesses and threats:***

The relative lack of experience of the team leader. However, mentorship support is available.

- ***Recommendations:***

The mentorship of Mr Marc Peschanski is important. Nevertheless, additional interactions could be useful for the group leader to extend her network or collaborators and to develop a fresh vision.

This group needs to maintain its focus on basic studies. This will be essential for future projects and for future publications.

The committee was very impressed by this group and marks it at the outstanding level.

Team 3 : Genodermatosis

Name of team leader: Ms Christine BALDESCHI

Workforce

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

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	1
Theses defended	2	1
Postdoctoral students having spent at least 12 months in the unit		1
Number of Research Supervisor Qualifications (HDR) taken	1	2
Qualified research supervisors (with an HDR) or similar positions	1	0

• Detailed assessments

Assessment of scientific quality and outputs

Team 3 has developed innovative protocols to generate keratinocytes and melanocytes from hESCs and hIPSCs. These protocols have been published in high impact journals (Proc Natl Acad Sci U S A. 2011, Lancet 2009) and are used by other groups worldwide.

They also uncovered novel mechanisms involving miRNA in epithelial skin cell differentiation.

This program of research has now move toward cell based therapy. A clinical trial is currently in preparation with a focus on sickle cell disease epidermis ulcer. Animal work has already been performed and GMP protocol is now available. The clinical trial should start in 2015. This is a major development with a unique interest at the international level. This group is leading this kind of application and this clinical trial will have a major impact in the stem cell field and beyond.

In parallel, this team is also developing an ambitious program of disease modeling and drug screening. They focus on a diversity of diseases including Neurofibromatosis type 1 and Epidermolysis bullosa simplex. This program of research is impressive and will generate important results. Only few groups in the world can achieve such screen on a diversity of cells. However, the interest to uncover basic mechanisms of disease is less obvious and might limit future developments.

Of note, an important part of their objectives will rely on the development of a protocol for generating Schwann cells from hPSCs. This objective is important and will be ground breaking if successful.

Assessment of the unit's academic reputation and appeal

The team has published several manuscripts in high impact journals such as Lancet, PNAS and Developmental Biology. However, the presentation of this work in international meetings has been limited. The team leader should be more frequently exposed to international evaluations and interactions.

The work generated by this group is important and will have an international impact especially the cell-based therapy clinical trial. However, this team would benefit to have more interactions and collaborations at the international level. Their achievement should be more broadly recognized.

Only a handful of clinical trials with hESCs are so advanced. This team is doing what a lot of laboratories/institute are only planning to achieve. This important experience could also be shared more broadly.

The work of basic mechanisms will also benefit from further exposition and collaborations. There are only a few groups working on skin development and diseases with hPSC and thus the achievement of this team should raise a lot of interest.

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

The team has established several contacts and collaborations with industrial partners including pharmaceutical companies. This team has filed 3 patents and this intellectual property represents an important asset for I-STEM.

The team leader is involved in several consortia for the clinical trial. Patient organizations are also involved.

Assessment of the unit's organization and life

Team 3 has a coherent organization with a strong focus on diseases affecting the skin and related organs. This team is fully integrated in I-STEM organization and its activity is essential for the success of the unit. The organization of the group is sound and seems to work well.

Assessment of the unit's involvement in training through research

The team hosts 4 PhD students who are well supervised. Their knowledge is well established and their technical training adequate.

Previous PhD students have been successful in securing post doc positions and have generally found a job rapidly at the end of their thesis.

The team takes part of the general organization of I-STEM and joins the regular meetings.

Assessment of the strategy and the five-year plan

The main objectives for the next five years are 1) Regenerative medicine of the epidermis using human embryonic stem cells derivates for skin ulceration complication sickle cell disease; 2) Disease modeling and drug screening of cellular markers of simplex epidermolysis; 3) Disease modeling on the neurofibromatosis type I. The five years plan is extremely ambitious but the underlying strategy is sound. The clinical trial will consume a lot of resources and times. This is expected and necessary. There is high level of uncertainty with this type of clinical trial which might be achievable or not and which might be successful or not. This is an inherent risk with clinical development but a backup plan or alternative strategy could be useful. Similarly, the disease modeling / drug screening program is rightly ambitious. However, it could be challenging to achieve all these objectives and some diseases/screening might have to be prioritized. The plan to study basic mechanisms of diseases is less clear and could be reinforced if time and resources are available. Importantly, this team is well organized and has been successful in the past. So, the expert committee thinks that this group will produce important results.

Conclusion

Team 3 is a strong group, which has already made an important impact in the stem cell field and has achieved major goals including the development of a clinical trial. Future projects are interesting and will lead to important results. The track record of this team is impressive. This group has made significant progress toward the use of hPSCs in cell-based therapy for skin ulcer. This is a unique focus and renders this group competitive at the international level.

- ***Strengths and opportunities:***

Cell therapy expertise.

Focus on skin.

- ***Weaknesses and threats:***

The lack of exposure of the team leader to international evaluation.

- ***Recommendations:***

The program on disease modeling/drug screening is impressive but could be further supported by more detailed studies on basic mechanisms. The objectives of this group in this area are less clear and could be more ambitious.

Additional interactions with external collaborators especially at the international level will be important to validate the strategy around cell based therapy but also for future development.

The committee was very impressed by this group and marked it at the excellent level.

Team 4 : Pharmacological approaches

Name of team leader: Mr Marc PESCHANSKI

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		1
N2: Permanent EPST or EPIC researchers and similar positions		3
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		8
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6		**12**

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

• Detailed assessments

This team is new and will start following the renewal of the unit. Therefore, only the five-year plan is assessed.

Assessment of scientific quality and outputs

NA.

Assessment of the unit's academic reputation and appeal

NA.

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

NA.

Assessment of the unit's organisation and life

NA.

Assessment of the unit's involvement in training through research

NA.

Assessment of the strategy and the five-year plan

The main objective of this team is to address the issues associated with primary drug screening. Indeed, identification of molecule at an early stage of development is useful but lead optimization is a major challenge requiring specific expertise and resources. This team aims to address this challenge by taking advantage of existing molecule, analyzing combinatorial effects, and repurposing existing drugs. This strategy is important to address an important limitation of drug screening and to ensure rapid drug discovery for rare diseases, which are not always of interest for industry.

Proof of principal has already been achieved with Metformin for DM1 but also for statin and Farnesyl inhibitor for Progeria. The plan is to extend this strategy using basic knowledge already available, developed by the other teams of the unit or by this team itself on specific disorders such as Wolfram syndrome.

Conclusion

The creation of this team is answering an important gap in the strategy of I-STEM and will be essential to achieve the translational objectives of this unit. Therefore this initiative is welcome and will bring an added value to the general organization of I-STEM.

- ***Strengths and opportunities:***

Drug repurposing.

Existing expertise.

- ***Weaknesses and threats:***

Lack of focus and cohesion.

- ***Recommendations:***

Scientific coordination with the other groups of the unit needs to be more defined. Overlap could create some confusion and decrease the impact of the other teams.

The activity of this team is also very broad without clear therapeutic focus. So, overall this team will have an important role but coordination is necessary to ensure that this team is working synergistically with the existing teams. The committee agrees that this creation of this new team is necessary and will be essential for the future success of I-STEM. Therefore this team and the corresponding project has been noted excellent.

5 • Conduct of the visit

Visit dates:

Start:	Friday 17th of January 2014, at 8 am
End:	Friday 17th of January 2014, at 5 pm

Visit site:	I-STEM
Institution:	I-STEM
Address:	5 rue Henri Desbruères 91030 EVRY Cedex

Conduct or programme of visit:

8h:	Closed door meeting - Presentation of AERES to the committee
8h25:	Presentation of the Committee to the lab
8h30:	Presentation of the lab, achievements and projects (discussion included)
	Mr Marc PESCHANSKI + Ms Cécile MARTINAT.

Scientific presentations by teams (presentation + discussion):

9h15:	team 1
10h05:	team 2
10h55:	Coffee break
11h15:	team 3
12h05:	team 4
12h55:	Discussions with the lab personnel (in parallel) Audience: Committee members, AERES delegate, without team leaders
	Technicians, PhD students and post-docs, Scientists
13h25:	Lunch/buffet with the lab
14h00:	Meeting with the representatives of the governing bodies, a representative of the graduate school
14h30:	Meeting with the management team. Audience: Committee members, AERES delegate
15h00-17h45:	Closed-door meeting. Audience: Committee members, AERES delegate

6 • Supervising bodies' general comments

Evry, le 15 Avril 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 : S2PUR150007906

Direction de la Recherche, de la Valorisation et du Transfert

Objet : Réponse au rapport du comité de visite de l'Institut des cellules Souches pour le Traitement et l'Etude des Maladies monogéniques

Monsieur le Président,

Nous avons pris connaissance avec le plus grand intérêt de votre rapport concernant le projet de l'Institut des cellules Souches pour le Traitement et l'Etude des Maladies monogéniques porté par Mme Cécile MARTINAT. 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.

UNIVERSITÉ D'EVRY VAL D'ESSONNE Présidence

M. Michel GUILLARD
Administrateur Provisoire

Bd François Mitterrand
91025 Evry Cedex
Tél. 01 69 47 70 00/78 00
Fax. 01 69 47 70 07

I-Stem
CURE THROUGH INNOVATION

INSERM UEVE UMR 861 I-Stem

Evry, April 8th 2014

We are very thankful to all the members of the AERES committee for their positive report. We'd like to clarify two points that have been raised by this committee:

1) Concerning the development of Next Generation Sequencing applications within the unit the committee stated that "*this part could be reinforced to enable broader number of applications. In house bio-informatics support could become necessary. Further expertise on RNA-Seq/ChIP-Seq could help to initiate new projects. The absence of in house bio-informatics support is a concern*."
   As explained during the audition when this point was raised, we completely share the views of the committee regarding the development of NGS at I-Stem. The implementation of this technology in the lab has been initiated within Team n°1. Initially we have decided to focus NGS applications on the development of quality control assay(s) to certify the genomic integrity of stem cells bank and medicinal product destined to research and clinical applications.
   We agree with the committee that beyond RNA-seq and Exome-seq applications currently developed, additional NGS expertise (e.g Chip-seq) could help initiate new projects. This is why Team n°3 and n°4 have already developed strong collaborations both with the national center of sequencing (CNG, Evry) and with the group of Dr. Auboeuf (INSERM 1052, Lyon) whose team is dedicated to bio-informatics analysis.
   The initial investment regarding NGS in the U861 has consisted in the purchase of the high performance sequencer (IONproton) itself and the dedication (full time) of a research engineer from the Inserm (IR1, Dr Nathalie Lefort). In 2014, the strong dedication of the U861 to the development of NGS applications will consist in the hiring of two full time engineers (Ms. Jarriche and Ms Guigue) put in charge of RNA/DNA sequences production and bioinformatic analyses, respectively. In this context, Ms Guigue will work part time in Dr. Auboeuf lab to complete her training in bioinformatics.

2) The second point that we would like to clarify concerns the following comment regarding Pr. Monville in Team n°1 by the AERES committee: "*The RPE sub team could become independent and could be better placed in an environment with strong focus on eye disease such the Institut de la Vision.*". This program of research is already independent and is fully under the direction of Pr. Monville. She has and will continue to direct these programs and to work in close collaboration with Dr Goureau lab in the Institute de la Vision.

Yours Sincerely,

Cécile Martinat

5 rue Henri Desbruères
91030 Evry
Tél : 01 69 90 85 20 – Fax : 01 69 90 85 21