I-STEM - Institut des cellules souches pour le traitement et l'étude des maladies monogéniques

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

I-STEM

University of Evry

March 2009

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Le Président de l'AERES	Section des unités de recherche
	Le Directeur
Jean-François Dhainaut	**Pierre Glorieux**

mars 2009

Evaluation report

The research unit :

Name of the research unit : INSTITUT DES CELLULES SOUCHES POUR LE TRAITEMENT ET L'ETUDE DES MALADIES MONOGENIQUES (I-STEM)

Requested label : INSERM

N° in case of renewal : U861

Head of the research unit : Marc PESCHANSKI

University or school :

Université d'Evry

Other institutions and research organization:

INSERM

Date of the visit :

January 19th, 2009

Members of the visiting committee

Chairman of the commitee :

Ms. Margareth BUCKINGHAM, Institut Pasteur Paris

Other committee members :

M. Yann BARRANDON, Ecole Polytechnique Fédérale de Lausanne

M. John DE VOS, University of Montpellier 1

M. Peter ANDREW, University of Sheffield, UK

Ms. Ellena CATTANEO, University of Milan, Italia

M. Pierre TIEBERGHIEN, University of France Comté

CNU, CoNRS, CSS INSERM, représentant INRA, INRIA, IRD.....) representatives :

Ms. Johanna CHLUBA, CNU representative

Ms. Fabienne ROLLING, INSERM representative

Observers

AERES scientific representative:

M. Frédéric FLAMANT

University or school representative:

Ms. Jeanine TORTAJADA, Université d'Evry

Research organization representative :

Ms. Catherine LABBE-JULIE, INSERM

1• Short presentation of the research unit

- Number of lab members: 34 including
  - 3 researchers with teaching duties
  - 6 full time researchers
  - 4 postdoctoral fellows
  - 11 PhD students, all with a fellowship
  - 10 engineers, technicians and administrative assistants
- Number of HDR : 4
- Number of PEDR : 1
- Number of students who have obtained their PhD during the past 4 years
- Average length of a PhD during the past 4 years; 4 years
- Numbers of "publishing" lab members: 8 out of 8

2 • Preparation and execution of the visit

The laboratory provided only an electronic version of the documents, which were fully informative. Due to transportation problem the visit program was delayed by an hour.

9h00 : Committee meeting

9h30-10h00 : General présentation by the director

10h00-11h00 : team1 – neurosciences

11h00-12h00 : team2 – Pathology of ectodermal derivative

12h00-13h00 : team 3- neuromuscular pathology

13h00-14h00 : Lunch break

14h00-14h30 : Leaving lab member

14h30-15h00 : visit of the lab robotic Platform.

15h00-15h30 : Meeting with students, post-docs, technical staff, scientists.

15h30-16h00 : Meeting with INSERM and University représentatives.

16h-17h30 : Committee meeting

17h30-17h45 : Committee meeting with director

3 • Overall appreciation of the activity of the research unit, of its links with local, national and international partners

General Scientific Comments

The unit has made remarkable progress in two years. Building a team of promising young scientists to direct the three main themes of the Unit, the Director has sought to focus I-Stem on areas of human ES cell research and therapeutics that are tractable and offer early promise of significant outcomes: (1) a regenerative medicine application focused on Huntington's disease and, (2) a drug discovery programme, focused on monogenic diseases and utilising mutant hES cell lines derived from PGD (pre-implantation genetic diagnosis) embryos. This focuses mainly on myotonic dystrophy at present, but will be extended to other neuromuscular diseases. Other lines of research on neurovascular disease, skin disease and retinopathies are also developed in this context.

Regenerative Medicine

While many groups around the world are attempting to develop regenerative medicine applications, the challenges are large. First, it is necessary to choose a clinical condition for which there is a real possibility of achieving a cure by transplantation of a single cell type – ideally a condition arising from loss of a single known cell type, in a defined location and with minimal structural integration, and for which no other treatment is available. Second, it is necessary to overcome the difficulties of developing methods for controlling the differentiation of hES cells to provide pure populations of the required functional differentiated cell types. While many groups profess to be focussing on regenerative medicine applications, few are well advanced in studies pertinent to conditions that meet both requirements. However, Huntington's disease does meet these requirements. It is a well-defined, incurable disease for which the group has previously established a proof of concept by transplanting foetal neurons and effecting a partial cure in several patients. Second they have established protocols for efficient derivation of striatal neurons. Even so, substantial obstacles must be overcome before clinical trials are contemplated, these include access to clinical grade hES cell lines, establishment of safety, including overcoming problems relating to tumour formation, and establishing conditions to avoid immune rejection.

High Throughput Screening and Drug Discovery

The use of hES cells in drug discovery and toxicology has been widely discussed but little has been achieved to date, in part due to the reluctance, until very recently, of the pharmaceutical industry to embrace hES cells. That has now changed and several big pharma companies are actively engaging in hES cell research: e.g. over the past year GSK has opened a research institute in Shanghai and invested substantial funds in Harvard University; in the UK, a Public Private Partnership between the UK Government and several big Pharma companies has led to the establishment of a company, "Stem Cells 4 Safer Medicine", to explore applications in predictive toxicology. However all of these have yet to deliver any outcomes. In the academic sphere the most notable work has been that of Sheng Ding at the Scripps Institute in California, where he has set up high through put screening (HTS) of mouse and human ES cells, and reported several compounds that affect ES cell behaviour. The other proposed facet of drug discovery applications of hES cells is the use of hES cells derived from PGD embryos carrying specific mutations. While a small number of labs around the world have the capability of both PGD and hES derivation, and several PGD-embryo derived hES cell lines have been established, few have yet married these to HTS approaches. I-Stem is certainly at the forefront, and possibly still unique, in having established HTS technology applied to PGD-hES cell lines, obtained by collaboration with groups in Brussels and Strasbourg. The initial results that they have achieved from application of HTS approaches to PGD-hES lines carrying the Myotonic Dystrophy mutation (DM1) are impressive and promising. It should be emphasised that this is a unique academic, high throughput, screening platform in the field of stem cells in France. The platform is entirely automated, and comprises a high speed medium and cell pipetting system, an incubator with automated handling of 96- or 384 wells plates, and several high throughput analysis systems such as those for image analysis, or fluorescence/luminescence measurements. The platform is steered by a dedicated team (3 persons) and has succeeded in overcoming the difficulties involved in applying HTP screening to hES cells. In the future, this technology will need to be adapted to the requirements of iPS cells. The aim is to screen RNA, gene (cDNA) and chemical libraries. At present, such screening is done on a small scale.

Specific Comments Re: human ES cell technology

1. Central Banking of hES lines : I-Stem has established a central facility to bank and quality control hES cell stocks. This facility applies commonly accepted standards of quality control (e.g. phenotytping based on the results of the ISCI project, and cytogenetics. The facility provides 'feed stocks' to the different research groups in I-Stem. This is a strong feature of I-Stem.

2. PGD-hES cell lines : I-Stem has already accessed standard hES cell lines from different labs., worldwide, and established strong collaborations with a group in Brussels for the provision of PGD-embryo-derived hES cell lines. The belgian lab has derived several such lines, including the three DM1 lines used by I-Stem in its studies to date. Others are in progress and links are also established with the similar PGD group in Strasbourg. These relationships appear to be complementary and stable with the PGD labs following different lines of research from I-Stem.

3. iPS Cell Lines : I-Stem is actively working on developing iPS cells, and is well aware of the potential problems that are evident at this stage of development of the technology. For example, it is known that, following transfection with retroviruses encoding the key genes responsible for re-programming, iPS cells with varying degrees of conversion to an ES cell-like state may be produced. There is also the possibility that integration of the transgenes may disrupt a key endogenous gene, so affecting the phenotype of the resulting iPS cells. It is essential to monitor closely the phenotypes of these cells by comparison with hES cells, and to monitor their capacity for differentiation. I-Stem is currently also proposing to monitor DNA methylation patterns, which is certainly an appropriate strategy.

4. Clinical Grade hES Cell Lines and safety concerns for regenerative medicine : Regenerative medicine and clinical application of its research is a stated goal of I-Stem. Application of the hES cell-derived striatal neurons for transplantation requires access to 'clinical grade' hES cell lines that will satisfy the requirements of the regulatory authorities. At present, the nature of those requirements remains uncertain. Several hES lines that might meet those criteria have been derived (e.g. Michel Puceat has such a line; ESI in Singapore has derived such lines), and programs have been established elsewhere to derive such lines (e.g. in the UK). Currently, the I-Stem research on striatal neural differentiation is being conducted with 'research grade' lines. Development towards clinical application is following the route already successfully followed by the group in earlier studies of foetal neuron transplantation into human patients. This route includes plans for trials on monkeys using allogeneic monkey ES cell derived striatal neurons. Nevertheless, the regulators will most likely require that some pre-clinical studies, including efficacy and particularly safety studies (e.g. purity of striatal neuron preparations, absence of contaminating ES cells, lack of tumorigenicity, genetic normality), are carried out with the exact hES cell line that will be used for clinical trials. Currently the I-Stem team has not acquired such a line, although they are aware of potential sources. Also, I-Stem does not seem to have a GMP facility for maintaining clinical grade hES cells and producing their required derivatives to a clinical standard. When to undertake these activities is a fine judgement call because of the expense involved, but it does need to be undertaken sufficiently early to permit timely clinical trials once the underpinning basic research is sufficiently developed.

Scientific Output

In its brief existence I-Stem has already filed a number of patents on hES cells and has a number of good publications. From the work presented, more papers, some of them potentially high profile, should be forthcoming.

4 • Specific appreciation team by team and/or project by project

Team 1 : Neurodegenerative diseases

The team has two targets, Huntingdon's Disease (HD) and stroke. The programme on HD is very competitive and extremely well developed. The most important achievement so far is in the development of a protocol to differentiate hES into striatal neurons. This protocol has been developed based on known events occurring in vivo, followed by attempts at reproducing them in vitro using distinct combinations of substrates, media and signalling molecules. Using this strategy, the group has been able to guide hES cells towards the production of Darpp32+ neurons in a quantity and of a quality never achieved so far either from human or indeed from mouse stem cell sources. This protocol now represents a key reference in the field. Transplantation of cells at the most suitable stage of the differentiation protocol has led to important results, such as the definition of in vitro conditions that allow the complete maturation of the grafted cells and their organization into patch-like structures. A drawback of the protocol is the presence of proliferating cells which will have to be addressed by future studies. A second asset of the team is in pathological modelling. The group is one of a few in the world to have developed procedures for the systematic molecular screening of PGD-hESHD cell lines. They have the technical skills necessary to handle a large number of hES cell lines, including those carrying a mutant gene, and have developed the relevant screening technologies. Their screening, with chromosomal analyses, has revealed a hot spot of genomic instability in non transformed non pathological human cells, a finding which has been reported in a major journal. A third research line is the development of a high throughput screening assay based on the REST/RE1 reporter. Also in this case they have already

developed the necessary technologies to adapt this cell based reporter assay to automated culture and screening systems for HD cells. Future studies will reveal the efficacy of the screening and of the selected target.

The group working on Stroke has only recently joined IStem and therefore this assessment is mostly based on its future plans. The main objectives are in the area of stem cell therapy and neuroprotective protein therapy. It is expected that their stem cell therapy approach will become competitive based on the extensive knowledge, technologies and novel cell lines developed for HD, although these cells will have to be readapted to new conditions to meet the requirements for stem cell therapy of stroke. More innovative is the protein therapy approach and the choice of a TAT-Xiap based assay. However, this is also a very competitive field. The group has already published one paper in 2006 but they should define stringent milestones to be achieved within a reasonable time period.

Overall, the substitutive cell therapy approach is well set for HD and in the process of being verified for stroke, which represents a more recent focus for IStem. The group should make sure they invest major effort in HD to validate their stem cell therapy approach. They have a competitive advantage here compared with other leading groups in the world and the community at large will benefit from this validation step. A number of issues have yet to be worked out, including the development of strategies to prevent tumour formation.

Pathological modelling is also well set for HD although dependent on only a few hES lines which carry the mutation (but more will be included in the future). The innovative TAT-XIAP approach holds a lot of promise not only for stroke but also for other diseases, including HD. This provides an example of how collaboration between the two groups can lead to novel strategies for HD and stroke.

NEURODEGENERATIVE DISEASES

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A	A

Team 2 : Monogenic disorders of ectodermal origin

This programme has two parts. One group is working on epidermal lineage determination from hES cells and genodermatosis. A second new initiative centres on the retinopathies.

A junior MCF with recognized expertise in the field of epidermal differentiation leads the team that has had to face the recent loss of its leader. Research projects aim at investigating the process of epidermal differentiation from hESC and using the model to study dystrophic epidermolysis bullosa genodermatosis, a horrendous genodermatosis. The team leader is building on her previous experience in the field, a strategy that is quite comprehensible for a junior group leader. However, it has a serious draw back: the originality of project is questionable and the team faces serious competition from the research units in which the group leader had trained, not to speak of a ferocious international competition. This said, some of the results recently obtained are extremely promising, if they are confirmed. The team, in its present format, has not yet published, which is expected from a group that was recently constituted; nevertheless, a patent has been applied for and a paper has been submitted. The team has significant teaching duties and is working hard to do good research. As a general comment, the team leader should be supported on condition that original avenues are investigated within the frame of the general project of hES cell differentiation.

Previously I-Stem groups have not addressed the issue of retinopathies and the possibility that hES cells could be used as a source of cells suitable for ocular transplantation to provide cures for various causes of blindness. This possibility is now included in the new programme in which the differentiation of hES cells to photoreceptors is envisaged. It is now widely recognised that the eye does present a suitable target organ for early application of regenerative medicine techniques based upon transplantation of hES cell derivatives. Many conditions leading to blindness are incurable and poorly treated; potentially few cells are required for transplantation, an important consideration since methods for expanding hES cells and their derivatives to large numbers of cells with genotypic and phenotypic fidelity are poorly developed; the eye is a confined organ, potentially immunoprivileged and readily accessible for monitoring the behaviour of any transplanted cells. Several groups around the world (in the USA, Israel and the UK) are currently working to develop transplantation of retinal pigment epithelial (RPE) cells for the treatment of Age-related Macular

Degeneration (AMD). AMD is an attractive first target since clinical proof of concept exists from transplantation of autologous RPE cells and since some hES cell lines appear to spontaneously differentiate in this direction. Applications based on development and transplantation of photoreceptors are a greater challenge since definitive protocols for photoreceptor differentiation from hES cells remain to be developed; nevertheless there is promising evidence that this may be feasible. Transplantation of photoreceptors also presents a greater challenge than RPW cells because of the need for integration into the neural network of the eye. So far, clinical proof of concept appears to be lacking. Thus a focus on photoreceptors represents a higher risk than RPE cells, though nevertheless a promising direction. The current plans of I-Stem are focused on photoreceptors rather than RPE cells, though it is possible that the pigment cells reported during the site visit in the context of epidermal differentiation, may be RPE cells rather than melanocytes as proposed.

The committee recommends that I-Stem should continue work in connection with retinopathies as planned and seek to develop protocols for photoreceptor differentiation from hES cells. At the same time they should explore whether any of their hES lines do differentiate into RPE cells. They should also seek to establish collaborative links with clinical ophthalmology units which might eventually exploit developments in photoreceptor and RPE cell differentiation based upon the planned basic research.

MONOGENIC DISORDERS OF ECTODERMAL ORIGIN

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	B	B	A	A

Team 3 : Neuromuscular Diseases

The aim of this team is to model neuromuscular disorders using human ES cell lines which carry the mutation that underlies the disorder and then to apply high throughput screening to search for sequences that reveal proteins or RNAs of potential therapeutic interest. They have initiated this approach with myotonic dystrophy (DM1) as a model. This common form of inherited muscular dystrophy is caused by the expansion of a trinucleotide repeat in the DMPK gene, which results in the accumulation of aberrant transcripts and major perturbation in the RNA processing machinery of the cell. This has repercussions notably on skeletal muscle and motorneurons. Using hES (DM1) cell lines isolated by a laboratory in Belgium, the team has obtained mesenchymal and neuronal derivatives which show classic biomarkers of the disease. A limitation at present is that they have not succeeded in deriving skeletal muscle cells. Having validated the model, they have carried out transcriptome analyses to look for aberrantly regulated genes in the DM1 ES cell derivatives. A concern, here is inherent variation between human ES cell lines. However this is at least partially obviated since they are looking for changes common to 3 independent DM1 lines and also go on to do validation on material (ex. muscle cell lines) from DM1 patients. Validation by over-expression and siRNA knock-down is part of their strategy. High throughput screens for modification of DM1 biomarkers, using siRNA libraries, have been successfully developed. These approaches have revealed a number of potentially interesting candidates, including genes involved in stress response, transcriptional repression and neurite outgrowth, as well as a microRNA cluster up-regulated in muscle fibers. In some cases they have begun to work out potential mechanisms. The difficulty here is having the appropriate expertise. Moving into mouse models for DM1, with candidate genes, for example, is not a trivial undertaking. Deciding when and with whom to collaborate is crucial. However they are aware of this and have already engaged in a number of collaborations. For their enterprise to be successful, handing over the candidate, even if painful, will be necessary, if they are not to be "side-tracked" into addressing questions of basic biology. For a young research scientist this can also pose a problem, since it is more satisfying and more straightforward, from a carrier point of view, to follow a project through to the end. At present this is not yet an issue, since exploration of candidates is still at an early stage. In this first phase, the group has done very well in setting up and validating the approach with hES cells in the DM1 model. They have begun to publish, and within a relatively short time they should have a number of results which when consolidated should lead to good publications.They propose to extend their approach in the future to other neuromuscular disorders, such as SMA, ALS or FHDG, where hES cells carrying the defect are available. It will be important to consolidate the DM1 leads, before producing a range of further disease candidates.

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	B	B	A

Cardiac Research

Work on ES cell derived heart cells at I-Stem will not be continued. However the committee would like to underline the contributions of one the team. They have carried out important research on the differentiation of ES cells into cardiomyocytes with some high impact publications. Since joining I-Stem they have identified novel markers of cardiac progenitor cells and have uncovered an unexpected role of Oct4 at the onset of cardiogenesis, when the Sox17 gene is an Oct4 target, replacing Sox2, implicated with Oct4 in pluripotency. Their expertise in ES cell culture was an important asset to I-Stem during the establishment of the Institute. However, the group leader plans to continue exploring fundamental aspects of cardiac cell specification in the ES system which is not altogether compatible with the goal of I-Stem and will therefore move his laboratory to an adjacent site, while maintaining contacts. The committee regrets this separation and encourages continuing technical and scientific collaboration. In the cardiac context, an I-Stem group has been engaged in research on potential hES therapy for cardiac insufficiency in Duchenne muscular dystrophy. Using protocols for ES derived cardiomyocytes they have examined their integration into organotypic tissue slices and also GRMD dogs. Some of these results look promising, however the dog model poses problems of survival and also involves a large financial investment (AFM). Their study will finish in 2009.

5 • Appreciation of resources and of the life of the research unit

It has been a remarkable feat to set up I-Stem so rapidly as a fully functional Institute. It is well organised and well financed. The 50% contribution to the core stem cell facility from the AFM is a major asset. However the director has also been very successful in attracting outside funding. The committee particularly commends the participation of I-Stem in a number of EU projects, and the success of its director as a co-ordinator and in placing I-Stem as an important source of hES cell lines for Europe.

The director has made an effort to recruit good young scientists at the postdoctoral level from the USA and elsewhere; their competitivity is indicated by their subsequent recruitment to posts in the research organisations/University of Evry. The close association with the University of Evry is of vital importance also in the recruitment of students and the committee encourages I-Stem to initiate new courses in stem cell biology/regenerative medicine.

The people working at I-Stem, - technicians, students, postdocs - seem very happy with their scientific environment. The difficulty comes from the relative isolation of the Institute/campus which does not have adjacent housing or facilities. In the near future, Evry and the University should envisage investments in this respect.

An important scientific preoccupation is the interface with the clinic. At present this can be done by specific interactions with specialists in Paris. However in the longer term a medical school and teaching hospital in Evry, would greatly increase the impact of I-Stem on translational research, with the possibility of training in regenerative medicine.

The Director proposes a rapid expansion of the Institute (x 2 the number). Although the vision of the Director has brought I-Stem to its current level in a short time, duplication of such a large institute is a big jump and the scientific elements justifying such a need are not evident now, although they may exist. I-Stem has succeeded in establishing itself as a credible institute. Firstly it would be important to consolidate this position and to follow up on promising leads already obtained, before acquiring too many others. Secondly, the success of I-Stem to-date has depended to a large extent on the direct scientific as well as administrative management one senior researcher in the Unit. A major increase in size will require the recruitment of more senior scientists and the delegation of responsibility.

6 • Recommendations and advice

— **Strong points :**

Impressive installation of the facility and of operational research groups in a brief time period. Promising first results.

— R**ecommendations : [Specific comments on research programmes are given in the appropriate part of Section 4].**

hES cells:

The central facility should join the International Stem Cell Banking Initiative (ISCBI), funded by the International Stem Cell Forum of which INSERM is a member. This would ensure continued contact with other groups and with developing standards in this area.

The central facility should exploit its position to engage in developing underlying technologies for hES cell applications such as development and production of advanced media and culture conditions (e.g. serum free, feeder free media, defined substrates).

PGD-hES cell lines:

The I-Stem groups should retain a focus on selected monogenetic diseases, particularly those relevant to its core interests, rather than expand its activities to cover all of the conditions that might be studied with the available PGD lines.

I-Stem is already actively setting up iPS technology which is an alternative way to PGD-hES lines for studies of specific genetic conditions. However, the iPS technology is still immature and presents both opportunities and problems; it remains complementary to work with PGD-hES cells, and both avenues should be followed.

The group is aware of the potential pitfalls in attributing specific aspects of the phenotypes of mutant hES cells or their derivatives to the specific mutation carried by the cells: for example, there are significant differences between

hES cell lines generally with regard to precise phenotype and differentiation capacity (differences probably both inherent and acquired during culture), while spontaneous differentiation or sporadic variations in differentiation from time to time, with resulting heterogeneous cultures, could lead to misleading conclusions if appropriate controls are not implemented. As the group currently does, such controls can include the use of multiple mutant and wild type

lines. Controls should also include efforts to eliminate heterogeneity in the ES or differentiated cultures by isolating specific cell types according to appropriate markers. However, the ultimate proof of a link between genotype and phenotype would be 'rescue' of mutant lines by transfection with wild type genes: this remains a challenging proposition with hES cells but should be considered when feasible.

iPS cell lines:

I-Stem should work towards adopting a set of defined criteria for accepting iPS cells into its programs. These criteria should included monitoring of differentiation potential by teratoma formation or other well-defined means. A focus on lines in which the transgenes are silenced should also be considered.

Clinical Grade hES Cell Lines and safety concerns for regenerative medicine:

I-Stem should soon seek access to potentially clinical grade hES cell lines and begin a program to establish a suitable bank of well characterised undifferentiated cells. Screening of these banked cells should include assessment of genetic normality, particularly assessing for chromosomal changes commonly seen in hES cell lines (extra copies of chr 12, 17 and X) as well as the changes that this group has recently identified on chromosome 20. The ability of these cells to generate striatal neurons according to the established protocols should be assessed.

Through it's commitment to bringing ES (or iPS) based regenerative medecine to the clinic, and in view of the considerable amount of expertise within the unit, this laboratory has a unique opportunity to tackle important safety and feasibility issues such as tumorogenicity and immunogenicity. The suicide gene (HSV-tk) approach is being considered as a "safety switch". Heterogeneity with regard to transgene presence and to expression (especially long-term) as well immunogenicity of foreign proteins such as HSV-tk are however significant hurdles to such an approach. Immune rejection of cells derived from allogeneic stem cells is another significant problem as confirmed by a first study by the group (PLoS ONE. 2007). Establishment of collaborations with research groups with relevant expertise in immunology is recommended.

High throughput screening and drug programmes:

Closer contacts with Pharma will be required to gain access to major chemical libraries, or to collaborate with them.

A policy of access to other academic teams should be envisaged, particularly since the facility does not seem to be operating full time - ideally this platform should be recognised by GIS Ibisa.

Institut des Cellules Souches pour le Traitement et l'Etude des maladies Monogéniques

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A+	A	A