Running over Roadblocks

France’s stem cell research policies are neither Europe’s easiest nor toughest but the country has managed to make progress in regenerative technologies, despite restrictions. The current bioethics law is up for review, suggesting change may be ahead.

By Céline Héchard

As European countries go, France is middle of the road when it comes to stem cell research using human embryos. Thanks to its bioethics law passed in 2004, France is less restrictive than countries like Italy and Portugal, where human embryonic stem cell research is illegal. But it’s not as liberal as places such as Britain and the Netherlands, where research policy is considered among the least fettered. Despite the restrictions, French scientists have managed to make significant progress in the field, thanks in part to constructive relationships with government, as well as the work of an innovative institute. And things are looking up.

The 2004 bioethics law, which actually softened a much stiffer policy established in 1994 forbidding any research requiring the destruc-
tion of a human embryo, is to be revised in 2010. A public comment period in 2009 is likely to shape revisions to the 2004 law, which essentially allows research on a very restricted basis using embryos conceived within the framework of certain assisted-reproduction techniques. Embryos discarded following pre-implantation genetic diagnosis for severe diseases of genetic origin, for instance, are allowed, but research cannot be performed without the prior written consent of the donor couple.

It’s unclear in which direction French policy will move, but what is certain is that the public comment period—and the subsequent policy debate—will play a big part in the revision of human embryonic stem cell research policy. A number of institutions including state agencies, ethics leaders, and religious groups are currently studying ways to modify the law. The current policy status of “forbidden with dispensation” essentially gives France’s Agence de la Biomédecine the right to grant authorizations for research on human embryos and human embryonic stem cells to applicants for a maximum period of five years. The regulation often resulted in the opinion, especially abroad, that stem cell research of substance in France was impossible. Although this is not true, the policy’s impact on investment in the field, both public and private, has clearly hurt. Nevertheless, researchers in France have produced results and research programs are under way in many labs in France.

The most accomplished project is perhaps I-STEM, the Institute for Stem cell Therapy and Exploration of Monogenic diseases, where I serve as director of business development and partnerships. I-STEM develops cell therapy and genetic diseases models for drug discovery. As of March 1, 2009, some 33 research programs have won permission to be conducted on human embryos or human embryonic stem cell lines. Most of the authorizations have been given to projects dealing with human embryonic stem cell line derivation or directly using human embryonic stem cells. The number of research projects...
studying the whole embryo being very small. Another 25 authorizations have been given for importation, and 11 sites have been allowed to store human embryonic stem cell lines.

The scope of research is broad, ranging from the analysis of mechanisms for pluripotency and differentiation, to modeling diseases, pharmacological screening, and technical projects (improvement of culture conditions). There are various research sites, including several authorized teams. Two-thirds of the teams are concentrated in the Paris region. In recent years, French researchers have tried to make up the time lost before the 2004 revision to the nation’s bioethics law. Results are building, and innovative research is being published. More than 10 human embryonic stem cell lines have been derived and characterized in France.

But leading the pack has been I-STEM. Marc Peschanski, research director at Inserm (the French National Institute for Health and Medical Research) jumped at the opportunity to develop embryonic stem cell research and began the I-STEM project in 2005. The institute’s mission consisted of building a research center in Genopole Evry, an area about 20 miles from Paris, dedicated to exploring the therapeutic potential of stem cells with regards to rare diseases of genetic origin.

The institute has benefited from France’s first authorization by the Agency for Biomédecine to import from abroad human embryonic stem cell lines in accordance with the current legislation. Inspected by the agency in June 2007, the institute as well as its labs, procedures, and programs all received positive reports.

“I-STEM’s genesis took two years,” says Peschanski. This proof-of-concept time was supported by Inserm, the University Evry-Val d’Essonne, and direct financing from the French Muscular Dystrophy Association. A positive evaluation by the scientific council, in 2006, allowed the continuation of the partnership between the institute and the association. The institute was officially inaugurated in October 2007. It is a public-private venture that encompasses two collaborating laboratories: the Inserm Unit 861 and the dystrophy association-funded CECS lab. The institute currently includes 10 research teams plus support services, with about 80 people made up of about 50 percent Ph.D. scientists and graduate students.

At the institute, teams are dedicated to research on the central nervous system, the retina, the motoneuron-skeletal muscle axis, the heart, and the epidermis. Three additional research groups are devoted to main technologies for functional genomics of stem cells, large scale banking of pluripotent stem cells, and high-throughput/high-content screening. The institute has focused on the development of treatments intended for monogenic diseases, founded on the strong potential of stem cells for substitutive and regenerative therapies.

The institute’s second goal is to develop disease models using human embryonic stem cell

MARC PESCHANSKI, I-STEM DIRECTOR AND FOUNDER/I-STEM
lines or induced pluripotent stem cells (iPS), each carrying a mutant gene associated with a given disease. These should help elucidate mechanisms of pathogenesis, and consequently, reveal possible therapeutic targets. These models could also be used as a basis for screening compounds libraries in order to discover new potential drugs.

On the drug-development process front, the institute has set up a department of high-throughput and high-content screenings through a partnership with the companies Velocity11 (now part of Agilent Technologies), Discngine, and Prestwick Chemical. At its site, the institute has installed a powerful automation platform using the Velocity11’s BioCel technology, coupled to a specific data management system designed by Discngine. The Ile-de-France Regional Council and the French Muscular Dystrophy Association co-funded this platform.

The institute’s more advanced cell therapy program centers around substitutive cell therapy: Production and assessment of the use of progenitors of GABA-ergic striatal neurons derived from normal human embryonic stem cells as grafting material for Huntington’s disease cell therapy. Cell therapy using fetal striatal grafts has demonstrated preliminary clinical success in patients with Huntington’s disease, but the logistics required for accessing fetal cells preclude its extension to the relevant population of patients. Human embryonic stem cells theoretically meet this challenge, because they can be expanded indefinitely, according to 2008 research in *Tissue Engineering Part C,* and differentiated into any cell type. Institute scientists designed an in vitro protocol combining substrates, media, and cytokines to push human embryonic stem cells along the neural lineage, up to postmitotic neurons expressing striatal markers. Human embryonic stem cells and human embryonic stem cell-derived cells quality is strictly controlled during all the production process, according to 2008 research in *Nature Biotechnology.*

The therapeutic potential of such human embryonic stem cell-derived cells was further substantiated by their in vivo differentiation into striatal neurons following xenotransplantation into adult rats. The results open the way toward human embryonic stem cell therapy for Huntington’s disease. Long-term proliferation of human neural progenitors leads, however, to xenograft overgrowth in the rat brain, suggesting that the path to the clinic requires a way to switch them off after grafting, according to 2008 research in *Proceedings of the National Academy of Sciences.*

The institute has just achieved a first pilot therapy-oriented innovative high-throughput screening and high-content screening of chemi-
The study is aimed at reversing the altered phenotypes observed in stem cells derived from a human embryo identified as a gene carrier for myotonic dystrophy type 1 during pre-implantation genetic diagnosis. Institute teams have shown that human embryonic stem cell lines carrying the mutant gene responsible for myotonic dystrophy type 1—the most frequent myopathy in adult—present known cellular and molecular abnormalities. Therefore, intranuclear foci formed by mutant RNA and aggregated proteins, which are responsible for the abnormal splicing of a number of other genes leading to most symptoms associated to the disease, are detected in these cultures.

Human embryonic stem cells’ capacity of self-renewal and pluripotency provides an unlimited and highly versatile cell resource, relevant for large-scale analyses, up to high-throughput and high-content screenings.

Using the high throughput platform, the institute teams have looked for compounds and short interfering RNAs or siRNAs that would provoke the disruption of intranuclear foci in the mesenchymal progeny of a human stem cell line derived from an embryo carrying the myotonic dystrophy type 1 mutation. Several of the 1,120 compounds and 50 siRNAs assayed were identified as “hits” in an assay based on the specific staining of foci using FISH (fluorescent in situ hybridization). The institute intends to
3. Research on embryos/human embryonic stem cells

Additionally, authorizations for importation or storage could only be given to teams that have received a research authorization. Academics or private companies can be entitled to perform research on human embryonic stem cells, provided that they have an agreement with a laboratory authorized to store these lines.

To be authorized, a submitted research project must fulfill the two following conditions:

1. They must be likely to bring major therapeutic advances (especially research on particularly serious or incurable diseases);
2. There must be no alternative treatment of corresponding efficiency in the current state of scientific knowledge.

Once submitted to the Agence de la Biomédecine, the projects are reviewed both by an internal scientific committee and an internal ethics committee for the following items:

- Scientific relevance of the research project;
- Conditions of implementation in relation to ethical principles;
- Relevance for public health.

Other criteria are also considered: feasibility of the research protocol and durability of the leading organization and the research team, strengths of the director of the project and its team, material and technical conditions (premises, equipment, facility, process, and techniques), safety, quality and traceability conditions of the embryos and cells.

The Agence de la Biomédecine is also entitled to conduct onsite inspections to check whether all these technical conditions are met. These inspections usually take place one year after the program has begun.

The public debate over upcoming revisions to the French law on bioethics is currently under way. A draft of the law is expected to be released before the end of 2009 and will be considered by members of parliament in 2010. There’s no question that France’s scientific community and its work will be impacted by any revisions to the law. The expected changes will come at a time when the stem cell field is seeing some major developments, including the U.S. Food and Drug Administration’s authorization of the first clinical trial using stem cells, as well as President Barack Obama’s easing of federal restrictions on research in the United States.

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The French Bioethics law of 2004 forbids:

- Any form of reproductive or therapeutic cloning (i.e. nuclear transfer);
- Any in vitro conception or any constitution by cloning of human embryo for the purpose of research;
- Any in vitro conception or any constitution by cloning of human embryo for industrial or commercial purpose.

Stem cell researchers initially complained that submitting a request for authorization was a very heavy burden, including exorbitant amounts of administrative work. While this cannot be denied, exchanges and practice between the Agence de la Biomédecine and the research teams seem to have smoothed the process. The agency is now seen by some as a partner that can provide some help in understanding the law and submitting requests for authorization under optimal conditions. Onsite inspections have notably been considered as ways to improve the safety and quality conditions that are not always obvious to implement. What’s more, most of the individuals in the field are aware that the high level of regulation relates to worries expressed by the public opinion—and that complying with it is the best way to ensure that research on human embryonic stem cells and embryos can go ahead after the revision of the law.