French Republic

THE PARLIAMENTARY OFFICE FOR SCIENTIFIC AND TECHNOLOGICAL ASSESSMENT

STEM CELL RESEARCH

Summary of the report by Messrs. Alain Claeys and Jean-Sébastien Vialatte, deputies

This report responds to the second referral to the Parliamentary Office for Scientific and Technological Assessment (OPECST) laid down by Article 26 of the Act of 6 August 2004 on bioethics. That Act lays down that 6 months before the end of the 5 year moratorium on the ban on embryo and embryonic stem cell research which it decrees, in other words February 2011, 'the Biomedicine Agency and the OPECST shall each draw up a report assessing the respective results of the research on embryonic stem cells and adult stem cells so as to allow a new consideration of these provisions by Parliament.'

This report follows on from those presented, in the OPECST framework, on bioethics Acts, and more especially that of December 2008 on the assessment of the afore-mentioned Act, and it also comes after the many OPECST studies on bioethics. It takes into account the debates held in various fora, the opinions of the Académies, the report of the State Council and that of the National Assembly Fact-Finding Mission, and the assignments, visits and hearings undertaken by the rapporteurs in France and abroad.

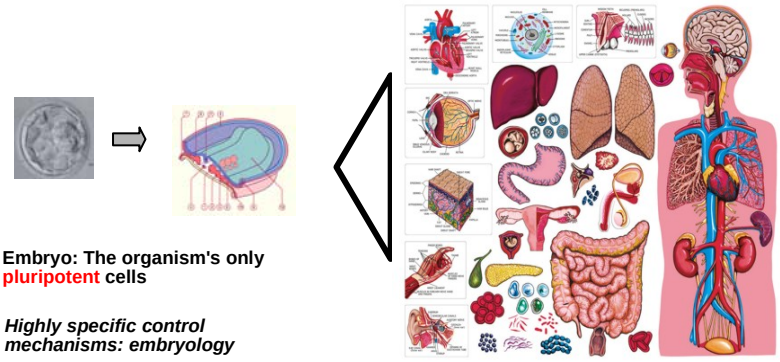
A few definitions

Human embryonic cells (hESCs) have the property of being totipotent stem cells until the 8-cell stage, then pluripotent from the morula stage to that of the blastocyst (from the 5.5th to the 7.5th day of development). There are several sorts of potentialities. Stem cells capable of differentiating into all embryonic and extra-embryonic cell types are totipotent. Those capable of producing, after differentiation, all the tissues of an organism, except for the embryonic annexes (placenta and umbilical cord...) are pluripotent. On the other hand, those that can supply a large number of cell types but not all, are multipotent. Those generating only a few cell types of a specific tissue are oligopotent, and those producing only a single type of cells capable of auto-regeneration are unipotent.

I – What advances over the past five years?

We now have the **complete identity card** of embryonic stem cells (ESCs), of adult stem cells (ASCs), and of induced pluripotent stem cells (iPS). Their properties are varied.

In vivo **: embryonic and foetal/adult stem cells: two different entities**
Source : Laure Coulombel : Public hearing of 27 January 2010



Embryo: The organism's only pluripotent cells

Highly specific control mechanisms: embryology

Foetus/adult: one type of stem cells per tissue

Survival, senescence, cancerogenesis

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A – Cognitive advances

1 – Progress on ASCs

Neural stem cells have been able to be cultivated *in vitro* from ASCs. Depending on the protocols, some divide and differentiate into neurons of various kinds. Intestine stem cells capable of producing mini-intestines have recently been isolated. It has been shown that the skin and hair follicle form a reservoir with broad potential for various stem cells capable of differentiation.

The importance of the *in vivo* environment of ASCs has been demonstrated. These cells are not independent; their normal operation depends on the components and structure of their tissue niches, as well as on their environment, which influences the success of their transplantation.

Highly studied, **mesenchymal stem cells (MSCs)** have given rise to questions and hopes as they can be easily multiplied from accessible tissues: bone marrow, adipose tissues, conjunctive tissues of the umbilical cord etc... Unlike ASCs which are tissue-specific, their function, cell of origin and physiological role *in vivo* are still unknown. By cultivating them *in vitro*, doesn't this induce properties that don't exist *in vivo*? They have an antiinflammatory, and antiseptic effect and induce immunotolerance allowing them to be transplanted allogenically to different patients.

Foetal stem cells, isolated from placental and umbilical blood, or from cord conjunctive tissue, have **specific properties recently highlighted**. They concern the production of cell growth factors, proliferation and immunology. **The need for the free 'solidarity-based' storage of placental blood in public blood banks** has been highlighted for allogenic purposes. Autologous transplants for the patient himself are scarcely prescribed as the treatments generally require stems cells from two cords.

2 - Discoveries on hESCs

The acceleration of **knowledge on pluripotency and multipotency mechanisms** allowed Prof. Yamanaka to discover **induced pluripotent cells (iPS).** He demonstrated that it was possible, without using gametes, to lead an ASC to adopt the properties of a pluripotent hESC; iPS are almost identical to natural pluripotent hESCs that can be cultivated and undergo a differentiation process. He isolated the 4 genes of pluripotency and paved the way for research on their mechanism of action. In a pluripotent hESC or an iPS cell, a large number of genes express themselves because the DNA structure is open. In an ASC, the DNA structure is closed and only the genes of the given tissue express themselves.

Reprogramming represents considerable scientific progress, which consists in passing from a closed to an open structure. This allows the differentiation, in a reproducible manner, of hESCs into different cell types (hepatocytes, neurons, cardiomyocytes, etc…).

Nevertheless questions **on pluripotency continue to exist.** iPS are not completely identical to hESCs and are believed to retain a memory of their tissues of origin. Derived from living donors, iPS are capable of being reprogrammed into gametes and could eventually pose ethical problems if they were used in human reproduction. hESCs therefore remain the reference for any comparative analysis.

The discovery of iPS shows that **no research must exclude any other and that research studies on ASCs and ESCs feed each other**. Therefore note must be taken of the interest the scientific community takes in all types of research. Also, the ethical problems which may arise from the use of each category of cells must be examined without any preconceptions.

B - What new applications?

1 - In fundamental research

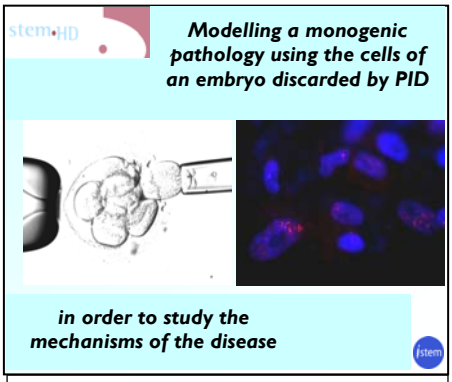
Comprehension of the mechanisms of the appearance and recurrence of some cancers (carcinogenesis) has progressed thanks to the studies on hESCs which, like cancerous cells, have the capacity to autorenew.

To make progress **in the field of medically assisted procreation (MAP),** the study of hESCs made *in vitro* abroad on preimplantation embryos at the blastocyst stage made it possible to distinguish those that were degenerating from those that could develop depending on the over- or under-expression of various proteins. This **research on embryogenesis** is necessary because it is unknown why 92% of embryos *in vitro* do not develop. In France, some research is considered as research on the embryo and therefore banned for use in MAP. This regulation applies to oocyte storage techniques like vitrification. **Therefore any technique aimed at improving the possibilities of *in utero* development of a human embryo should be considered as a medical procedure and not as research.**

2 - In pre-clinical research

Using hESCs from embryos that have been detected, within the framework of preimplantation diagnosis (PID), as carrying an especially serious

disease, **models** of stem cells are created that represent these pathologies in order to directly test various treatments or molecules. For this purpose, use can be made of iPS having an anomaly responsible for cancer, or a neurodegenerative or genetic disease. Collected from a patient, these iPS are close to his physiological reality, which allows personalised medicine solutions to be envisaged.



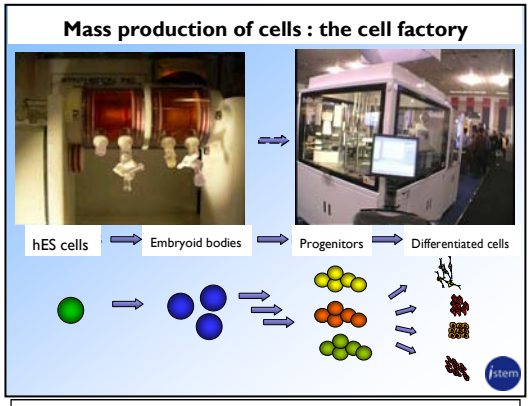
Source : public hearing of 27 January 2010 – M. Marc Peschanski

Screening is carried out on human stem cell lines to identify problems of toxicity and the degree of efficacy of a therapeutic molecule. The aim is to guard against undesirable or even harmful effects which do not always appear in animals, the use of which is tending to be reduced. Also, **various molecules are tested on a wide scale** on a broad and specific panel of stem cells of healthy and sick persons, and their effects are studied.

3 - Towards new clinical strategies

The use of robotisation and of adapted instruments and procedures have led to a change in scale. Up to one billion cells are cultivated in a fortnight. Nowadays, thanks to surface markers and flow cytometry, a minority population of cells can be identified in a tissue. These are given the necessary traceability to understand their role and ensure effective monitoring. Research on biomaterials, tissue engineering and direct medicinal action can be combined to stimulate *in situ* the components of the cell environment and speed up transplant repairs.

The existence of a far broader variety of utilisable cell types and the confirmation of the plasticity inherent in a number of cells allow **a wider variety of clinical strategies** to be envisaged: adaptation of the cell therapy product to the targeted pathology, adaptation of the type of administration (injection, patch, encapsulation), specific preparation strategy, etc... Several stem cell populations and complementary cells can be combined in a more functional transplant.



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In clinical practice, only **bone marrow cells and umbilical cord cells** and, more recently, **skin stem cells** are used. The latter are effective on the acutely burnt, the irradiated, and chronic wounds, by **direct action** on the affected area. They are also effective **by indirect action** on the environment of the affected areas; the contribution of these cells inhibits the immune response, induces a specific tolerance and facilitates the transplant of other tissues.

As for the use of embryonic stem cells, **four pre-clinical studies are under way**: three American studies, two on macular degeneration and one on the spinal cord which received its first clinical application at the beginning of October 2010; and one pre-clinical study currently being prepared in France by Prof. Menasché on heart muscle repair.

Numerous challenges to be taken up

***In vitro*, the future use of hESCs in clinical practice** requires perfect control over their cultivation conditions. The characterisation and standardisation of culture media must be achieved. The aim is to assure their genetic stability during their proliferation in order to combat malignancy, guide the stem cell differentiation processes, and produce them in a large quantity and reproducibily.

In vivo, it is necessary to manage, on the one hand, the behaviour of hESCs, once injected, by mastering their administration procedures and, on the other hand, the relocation of these cells, while solving immune problems.

Once cell reprogramming has been mastered, autologous transplants obtained from the patient's cells will, on the face of it, become more accessible.

This will pave the way for personalised regenerative medicine. However, the use of iPS in clinical practice will require a certain length of time.

II -Ethical and legal debates on this research

A- Varied approaches at the international level

The map of research on stem cells distinguishes **three categories of countries depending on their research policy**. It can be **permissive** (Australia, Belgium, China, India, Israel, Japan, Russia, Spain, Sweden, Taiwan and the United Kingdom) or else **flexible** (Brazil, Canada, France, the Netherlands, Norway, Switzerland and the United States). A **restrictive policy** banning this research is applied in Austria, Germany, Ireland, Italy and Poland.

Possibilities are appearing for the **harmonisation of regulations on research procedures**. More than 500 lines of hESCs have been derived, characterised and shared between various laboratories. High variability of the lines has been observed; a degree of reliability is limited to a few. Thanks to iPS, new lines can be created. That's why it would be useful to create **an international bank accessible to researchers and centralising and distributing lines**. It would be an interlocutor for national and international bodies, simplifying administrative steps and broadening the possibilities of research and exchanges. In effect, at the international level, research on hESCs is framed by the guidelines of the *International Society for Stem Cell Research* from which France could draw inspiration in regulating its research on hESCs. Compliance with these guidelines indeed conditions most international exchanges in this field.

The issue of patents is worrisome owing to divergences of legislation and of interpretation of the notion of 'living organisms'. The American Patents Office accepts to patent stem cell lines at the risk of leading to a merchandising of living organisms, which is refused by the European Patents Office and the National Institute for Industrial Property (INPI) in France. Therefore compliance should be ensured with the **principle that only the process and its application can be patented**.

B – At the national level, the law lays down a principle of prohibition combined with derogatory provisions

The human embryo enjoys justified legal protection, its future is dependent upon the parental project and, in the last instance, in the event of voluntary or medical termination of pregnancy, on the mother's decision.

The legislator of 2004 wanted to avoid the instrumentalisation of the *in vitro* embryo by affirming a principle of the ban on research combined with a derogatory regime lasting 5 years. A derogation is obtained after the Biomedicine Agency (ABM) authorises research likely to allow major therapeutic progress that cannot be pursued by an alternative method of comparable efficacy. This system has been operative thanks to the remarkable work by the ABM which, as of 31 December 2009, had issued 122 authorisations and 7 refusals. **A broad consensus is arising in favour of the lifting of the moratorium which expires on 5 February 2011**.

To reconcile ethics and research freedom, the legal regime of research on embryos and hESCs in France must be clarified as it lacks clarity abroad. It is however essential to increase international cooperation in this highly globalised field.

It would be beneficial to switch from a regime banning this research to one authorising it in a strictly framed manner. In agreement with the *Académies* and the State Council, but contrary to the Fact-Finding Mission, Messrs. Claeys and Vialatte recommend such a legal regime. Any authorisation issued by the ABM would be subject to a 'scientific and medical' aim and to the scientific relevance of the project. Reference to the term 'therapeutic' should be abolished as research on hESCs also has a cognitive aim.

For Parliament to act as an ethical watch-dog and assess the situation, **the rapporteurs suggest that the ABM should present its annual activity report to the OPECST** and that, on this occasion, it should draw up an annual assessment of the research authorisations on hESCs.

The rapporteurs recommend that **the framing of research be limited to embryonic stem cells alone** and that **already differentiated stem cells be excluded from this framing**, the initial application having already been authorised.

As for consent to embryo donation for research, which can currently be revoked at any moment, it would be better to **organise precise information for families on the research** that will be conducted and **limit the possibilities of revoking consent once research has started**.

Reconciling freedom of research and respect for the human embryo has been the goal of the rapporteurs who have therefore taken up and continued the work by the OPECST on bioethics.

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