Sponsors of human embryo research have become cautious, opponents of this research seized by the progress of teams using embryos and a series of contradictory publications: the position of the scientific race for the therapeutic use of stem cells is now difficult to establish for the uninitiated. Which teams working with adult stem cells, iPS cells or embryonic stem cells are more effectively progressing towards treatment?

Génétique presents this month an analysis by Professor Alain Privat, neurobiologist and corresponding member of the Academy of Medicine, and explores two particular cases that have animated science news in the past weeks: cell therapy for heart disease and “therapeutic” cloning.

Advances in biomedical research and clinical medicine without the use of human embryos

By Prof. Alain Privat

Considered by the Commission of Social Affairs and Health during the debate that led in July 2013 to the liberalisation of embryo research in France and, more recently, by the European Commission as a scientific expert under the One of Us initiative, Prof. Alain Privat insists that medicine does not need to use human embryos to treat patients. Here are his explanations.

G.: Is your opposition to human embryo research ethical or scientific?

Prof. Alain Privat: Both. The physician’s role is to heal to the best of his ability whilst keeping in mind an absolute safeguard: respect for human life. Research using human embryos that promises potential therapeutic solutions already crosses an ethical barrier; in addition, it is a mistake to invest precious time and money in a field that has led clinically to dead ends for two decades.

G.: Can you explain how human embryos are used today?

Prof. Alain Privat: Potentially, there are three areas: basic research on embryo development, the use of embryos for disease modelling, and drug screening for the pharmaceutical industry and research targeting therapeutics directly (cell therapy is a component of regenerative medicine). Let us say at the outset that the first two areas, called embryology, are mainly, if not entirely, conducted today in animal models (flies, primates, fish, chicken, rats and mice). In the pharmaceutical industry, the debate is currently closed, even to sponsors of human embryo research: for this use, iPS (induced pluripotent stem cells or inducible adult cells) cells, which have earned Professor Yamanaka the Nobel Prize(1), have the same properties as human embryonic stem cells (hESCs). They are easy to use, expandable in very large quantities and present no ethical barriers. However, their cost is a real problem: they are more expensive than stem cells extracted from human embryos, which are... free. If scientific pragmatism tends towards iPS, economic pragmatism (short-term) is hesitant: the development of a drug today, regardless of the nature, requires a decade of research involving particular lengthy and expensive animal testing models before proceeding to the stage of clinical trials on patients. The use of large numbers of cells derived from human embryos allows the pharmaceutical industry to perform wide-scale testing of future drugs at a lower cost than in animal models or iPS cells. This is one of the subjects of the contracts between the Swiss group Roche, and the ISTEM laboratory, created for this purpose by the AFM contracts.

In terms of regenerative medicine, the scientific debate remains open although from my point of view, the situation is even clearer. Finally, this last point is obviously the best example that incites possibilities in terms of care and justifies the means employed (destroying embryos) to produce the expected results (treating patients through stem cells extracted from embryos).

G.: On this last area and before going into details, can you remind us what regenerative medicine that we hear so much about is?

Prof. A.P.: This concerns replacing deficient cells, such as those producing insulin in the pancreas that are impaired in diabetes, or providing them with growth or survival factors.

The research makes use of cell and tissue therapy (transplants) based on stem cells. These undifferentiated cells are present in large numbers in embryos, but also, although more rarely, in most adult tissues.

Stem cells have two unique characteristics: they can multiply almost endlessly and they can also differentiate into all cell types of the adult organism.
G.: Going back to your position on cell therapy: what elements allow you to be so categorical?
Prof. A. P.: On the one hand, physicians have long used human adult stem cells, particularly those derived from bone marrow, which contribute to effective therapies in some haematological diseases, but also in other pathologies. Stem cells from the umbilical cord are also a valuable source. On the other hand, researchers have now since eight years an exceptional tool that I just mentioned: iPS. These cells can be grown, multiplied and used for all kinds of research with real therapeutic perspectives. In particular, they have the advantage over embryonic stem cells of opening the door to personalised medicine. Taken from patients with genetic diseases, they can be used to analyse the details of these patients’ specific pathology and to develop appropriate pharmacological, cellular or molecular therapies. This is obviously impossible with embryonic stem cells taken, by definition, from a different individual. Amongst the objections raised against iPS cells, the most common are the risk of tumour formation, and the inherent risks of using viruses to transform these cells. Recent literature describes the replacement of viruses by safe chemicals. Furthermore, the risk of tumour formation can be eliminated by cell-sorting techniques.

In summary, criticisms of the first generation iPS are pushed aside by the second generation of these cells. Moreover, even if in France the debate remains closed, numerous scientific teams cannot be mistaken: since 2006, nearly 3,000 scientific papers on iPS cells have been published in specialised journals. Over the past three months, the pathologies studied cover Parkinson's disease (Doi et al., Stem Cell reports, 2014), diabetes (Holdich et al., Transl. Med., 2014), fragile X syndrome (Doers et al. Cell. Dev., 2014) and Pompe disease (Higuchi et al. Genet. Metab., 2014). In addition, fundamental research on such developments has been conducted on primate iPS cells compared to human cells (Wunderlich et al., Stem Cell Res., 2014). Finally, clinical trials are already underway in Japan, for a serious vision disease, age-related macular degeneration (AMD).

However, since 20 years, no therapeutic approach using human embryonic stem cells has been successful. One of the most recent, conducted in the United States by the company Geron, was discontinued after a few months due to lack of convincing results.

(1) Prof. Yamanaka demonstrated that the introduction of four genes in adult mouse cells transformed them into stem cells. A year later, he reproduced the experiment on human cells.
Cell therapy for heart disease and therapeutic cloning: will embryos re-enter the stem cell race?

Two particular cases have resulted recently in several publications that seem confuse the issue of the use of stem cells for therapeutic purposes: cell therapy for heart disease and "therapeutic" cloning. Génétique presents an insight into the scientific literature to unravel the real progress from the hype.

Cell therapy for heart disease:
a great deal of attention...

The heart, like the brain, unsurprisingly stirs the interest of scientific teams. Recently, the prospect of caring for the victims of heart failure by stem cell injections has found new resonance in two almost simultaneous publications published in the scientific journal Nature.

The first publication emphasises the fact that the scientific literature on cell therapy for heart disease using a protocol based on adult stem cells does not present any benefits and if any benefits are found, they are due to study bias. The second publication appears to present, a priori, progress in the use of embryonic stem cells to treat heart failure and especially the decreased risk of developing tumours after injection of these cells, the most common risk when using embryonic stem cells. Can we infer that adult stem cells, until now more advanced than embryonic stem cells for heart therapy, will be undermined? In reality, we cannot.

Adult stem cells (haematopoietic and mesenchymal stem cells, therefore non-embryonic) have been used for myocardial regeneration after heart failure for a long time. Slight, but significant improvement of ventricular function has always been recorded after injection of mesenchymal stem cells derived from bone marrow. This positive post-infarction effect - increased ventricular ejection, reduced mortality and overall improvement one year after treatment - is clearly demonstrated in the most recent studies.

The reliability of adult stem cells is questionable. The article by Nowbar et al. casts doubt over adult stem cells, not about the effect of these cells in the treatment of heart failure in humans, but about the inaccuracies encountered in some reports. Concerning the effects, moderate though significant, presented in the preceding paragraph, the conclusions of this article need to be put into perspective.

The article that presents the progress on embryonic stem cells does not offer much in an area that matters now: results in patients. It demonstrates regeneration by cardiomyocytes derived from primate heart embryonic stem cells. Up until now, this has only been shown in mice, so the use of the rhesus monkey is not trivial. However, the article warns about the possible complications of such a procedure, in particular arrhythmias. As cardiomyocytes derived from embryonic stem cells cannot be injected into patients without the risk of immunological rejection, the study does not predict major changes in the field of myocardial regeneration in patients using stem cells unless an institute decides to undertake a clinical trial with cardiomyocytes under immunosuppressants, which from a regulatory point of view, is far from feasible.

A recent interview in Figaro Santé by Prof. Menasché (May 5), an ardent advocate of the use of human embryonic stem cells in cardiac therapy, also concludes by a review for the least cautious about the therapeutic use of these cells.

The real question remains as to why research in the field of iPS is not moving faster? Indeed, pluripotent stem cell therapy in humans is much more influenced by the issue of immunological rejection than by tumour development. Thus, logically, treatment by iPS derived from the patients themselves should prevail. A paper published in Nature Medicine in mid-May could also open up new perspectives: Harvard teams combine iPS, cell engineering and gene therapy to restore the myocardium in persons with a genetic disease leading to heart failure. This prospect should be followed closely.

Therapeutic cloning: the return?

Several recent announcements have demonstrated that therapeutic cloning in humans is possible. The reflections in the press are partly understandable by the contrast to the silence surrounding this research since the scandal of the Korean professor Hwang 2005. Does this mean that therapeutic cloning could again compete with other means of obtaining pluripotent
stem cells (iPS in particular)? Just to recall, the cloning technique extracts the nucleus of an oocyte and replaces it with the nucleus of a cell taken directly from the patient in need of treatment. Oocyte division is initiated to reach an early stage embryo from which stem cells are extracted.

The objective is to produce tissue genetically identical to the patient that would circumvent the rejection observed with "classic" embryonic stem cells.

An initiative that remains ethically untenable, expensive, and limited in terms of its application. Recent studies show that therapeutic cloning is possible in humans. However there are many obstacles. First, this technique involves creating embryos, thus humans for research, which is ethically indefensible. Next, the conditions are very precise, and with limited effectiveness. Success has theoretical interest, but has little practical applicability, especially for regenerative medicine. Reduced availability of human oocytes, ethical issues raised by paying women who donate their eggs and concerns of the abysmal society that represents human cloning, the low efficiency of the nuclear transfer procedure and the long time required to obtain doubling of the human embryonic stem cell population constitute the barriers that make difficult the application of such a technique as a routine procedure in the clinical field.

We know that the publications in this field are always accompanied by extensive media coverage. However, this is far from proving that "therapeutic" cloning has become a credible alternative to the use of iPS cells, more discrete, but already widespread and useful in laboratories.

(5) Irregularités du rythme cardiaque
(7) 2013 par M.Tachibana, S.Mitalipov et ses collègues de l'Oregon National Primate Research Center (USA), de la réussite du clonage thérapeutique sur des cellules humaines, suivie ce mois-ci de deux annonces identiques par deux équipes différentes, l'une Coréenne (Young Gie Chung et Dong Ryul Lee de l'Université CHA de Séoul), l'autre américaine (Dieter Egli et collaborateurs, au New York Stem Cell Foundation Research Institute).