Ethical reflection on the latest biomedical experiments by Juan Carlos Izpisua and his group

Over the last few days, some of the biomedical experiments conducted by Juan Carlos Izpisua and his group — in which researchers from several Spanish universities take part — have been widely reported by various media.

Let us say at the outset that we see no need to highlight the biomedical importance of these experiments (some of which we would dare describe as spectacular), as this has already been abundantly emphasised by the media. Quite another matter is the possibility of being able to use what they have achieved in human medicine, which could take several years.

The bioethical aspects of these experiments have scarcely been addressed, however, and we believe they merit consideration.

Before we go any further, and in order to structure this report, the experiments by Izpisua to which we are referring should be divided into three groups. Concisely (although we will refer to this in more detail below) they are: a) to create quasi-human organs in animals, to be ultimately used for clinical transplants; b) to modify the CRISPR technique that offers so many biomedical possibilities, to make it more efficient, and c) to apply cell reprogramming "in vivo", to try to rejuvenate a group of experimental animals.

1. **To create quasi-human organs in animals.**

These experiments were first reported in an article published in *Nature* in May 2015. They essentially consist in injecting human embryonic stem cells into mice so that they can generate quasi-human organs, since the human cells injected into the animal will produce organs with a genome that is very close to the human one. As already mentioned, the ultimate aim is to be able to use these organs in clinical practice, because as we are all aware, there is a shortage of organs available for transplant. If this could be achieved, it could undoubtedly be of great medical benefit.

A further step taken in this same respect by Izpisua himself is to try to create genetically modified animals that lack a specific organ, so that after injecting them with the appropriate human cells, they could generate that organ and, consequently, its human characteristics would be much more significant (see HERE). The biomedical importance of these studies needs no emphasis.

Nonetheless, *these experiments have objective ethical difficulties*, primarily that some of them use human embryonic stem cells which, as we know, require the destruction of a human embryo, making this practice ethically unacceptable.

It would be ethically very positive if investigators were to stop using human embryonic stem cells in future experiments, using iPS cells instead. Moreover, from a biomedical perspective, we believe these would be much more useful: since the cells to be transplanted come from the patient himself, potential problems with immune rejection would be drastically reduced. In fact, this is the investigators' ultimate goal. "If we can tell the human iPSC in an animal host to develop into a kidney or other organ, for example, it could provide an entirely new source for transplant tissues", says Izpisua (see HERE).

However, in addition to the previously mentioned ethical difficulty, these experiments also present another major ethical concern, namely that, for the time being, *colonisation of the human*

cells implanted in the animal in organs other than the one to be produced is not fully controlled (see HERE), and moreover, this colonisation could even reach the animal's brain. If this were to happen, animals could be generated with a quasi-human brain, and this, regardless of whether embryonic stem cells or iPS cells are used, has negative ethical implications. The potential to colonise the reproductive organs is also worrisome, since it could eventually result in the generation of human gametes in the animal. As a result, human gametes could be obtained from two animals of a different sex, and from these, a human being. This is ethically unacceptable.

We hardly need stress the ethical difficulty that this entails, which in September 2015, led the United States National Institutes of Health (NIH) to announce that they would not fund research in which human pluripotent cells were introduced into non-human vertebrate animal embryos, while they considered a possible policy revision in this area (see HERE). However, a group of American investigators published a letter in *Science* which they expressed their opposition to curbing these experiments. Eventually — and as yet without solving the problem — in September 2016, the NIH awarded Izpisua a grant that guarantees up to 2.5 million US dollars to cover the direct costs of these experiments for 5 years…

Apart from the above, Izpisua's group is continuing with this line of research, even using larger animals, especially pigs, in the hope that the organs created might be more useful in human medicine due to their larger size (see HERE).

As far as we are aware, the experiments with pigs (as regards both animals that can be called "wild-type", i.e. not genetically modified, and genetically modified animals) have not yet been published but, according to one member of the research group (see HERE), "seven piglets" with quasi-human organs have already been produced.

In summary, these are experiments that offer great biomedical prospects, but which also present *objective ethical difficulties*.

2. **Experiments to try to make the CRISPR technique more efficient.**

As is well known, the CRISPR system is an innovative biomolecular technique based on a natural bacterial system of adaptive response to viruses, used to perform programmed gene editing in different cell types.

However, this technique has difficulty integrating transgenes into non-dividing cells, which compose most adult tissues. Now, Izpisua and his group (see HERE) have proposed a modification that essentially consists in combining CRISPR with a gene repair system present in the cells themselves (non-homologous end joining or NHEJ), obtaining a personalised insertion package that they call homology-independent targeted integration (HITI). As proof of concept of the therapeutic potential of the method, its efficacy in improving visual function in rats with retinitis pigmentosa was demonstrated.

From a biomedical point of view, this is an unquestionable advance, but the use of human embryonic stem cells to achieve these goals makes these experiments ethically unacceptable.

3. **Application of cell reprogramming "in vivo" to prevent aging.**

Also in a recent article, in the prestigious journal *Cell* (see HERE), Izpisua and his group developed a technique which, in principle, applied in mice, seems to have achieved certain rejuvenation of the animals.

The technique basically consists in performing partial cell reprogramming "in vivo", expressing the four Yamanaka genes (Oct3/4, Sox2, c-Myc and Klf4) (see HERE) in short intermittent cycles. Complete cell reprogramming "in vitro" does not pose any problems, but "in vivo" it causes tumour formation. Induced partial cell reprogramming in mice avoided this, and the cells maintained their identity while losing the chemical markers of aging. Thus, researchers were able to improve cardiovascular and other organ function, counteract the signs of aging and increase the lifespan of the animals by 30 percent. Nonetheless, while this breakthrough seems promising, the investigators point out that, due to the complexity of aging, these therapies could take up to 10 years to reach clinical trials (see HERE).

This technique does not present any specific ethical drawbacks, since it does not use human embryonic stem cells, so, in principle, assessment of its use need only consider the possible biomedical benefits that might be obtained. While it is certainly legitimate to seek to endow our living years with the best quality of life possible, questions arise as regards the point to which it is reasonable to lengthen life expectancy, since social and human problems could result from this form of *enhancement*.

Summary

In summary, therefore, there are three different groups of experiments. The first two, if evaluated ethically from a utilitarian perspective — something defended by many of those who support them — could be used without any ethical objection, but if this evaluation is carried out from a personalist bioethics, **they present serious ethical problems, since biomedical benefit is put before human dignity. The third, regarding the prevention of aging, has no direct ethical difficulties but nevertheless raises indirect concerns, if its application encourages *enhancement*.**


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