

## LATEST RESEARCH BY JUAN CARLOS IZPISUA'S GROUP: BIOETHICAL ASSESSMENT

There is no doubting the importance of the biomedical research carried out by Juan Carlos Izpisua and his team. Their work is focused mainly on: a) the production of hybrids or human-animal chimeras ([https://www.cell.com/cell/fulltext/S0092-8674\(16\)31752-4?returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867416317524%3Fshowall%3Dtrue](https://www.cell.com/cell/fulltext/S0092-8674(16)31752-4?returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867416317524%3Fshowall%3Dtrue)); b) the development of methods to make the CRISPR technique more efficient (<https://www.nature.com/articles/nature20565>); and c) *in vivo* cellular reprogramming to prevent aging ([https://www.cell.com/cell/fulltext/S0092-8674\(16\)31664-6](https://www.cell.com/cell/fulltext/S0092-8674(16)31664-6)). Now, however, the group has expanded its research objectives to the production of human embryoids for use in biomedical research.

While all these research fields have undeniable importance, both medical and social, they also raise objective bioethical concerns.

### **Human-animal chimeras**

The group's experiments for creating hybrids or chimeras were first published in May 2015, in an article in Nature (<https://www.nature.com/articles/nature14413>). Essentially, they consisted of injecting human embryonic stem cells into mouse embryos so that they could generate quasi-human organs, which could be used for transplantation in human clinical practice. However, given the difficulty posed by the size of these organs, since they were experiments in mice, in 2017 they produced human-animal chimeras with larger animals (pigs and cattle) ([https://www.cell.com/cell/fulltext/S0092-8674\(16\)31752-4?returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867416317524%3Fshowall%3Dtrue](https://www.cell.com/cell/fulltext/S0092-8674(16)31752-4?returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867416317524%3Fshowall%3Dtrue)).

### *Bioethical Implications*

Obtaining **human-animal chimeras** [<https://www.observatoribioetica.org/?s=chimera>], i.e. animals that house human cells, and possibly in the future also tissues and organs, has great potential for biomedical research, but above all for the production of organs for transplantation. Nevertheless, irrespective of their biomedical interest, these experiments present objective bioethical issues, which can be summarized as: a) some of these experiments use stem cells from human embryos, which must be destroyed in order to obtain them;

b) the potential for the human cells implanted in the animal to colonize organs other than the one they are intended to produce is not fully controlled; c) such colonization could even reach the brain or reproductive organs of the animal receiving the transplant (<https://www.scientificamerican.com/article/tissue-mash-up-a-q-a-with-juan-carlos-izpisua-belmonte/>), which would add a further bioethical difficulty; d) the threat to the conceptual, social and moral boundaries that distinguish human beings from other creatures; and e) biosafety and animal welfare issues.

These ethical problems have led to an international consensus calling for termination of pregnancy of the chimeric animals at 14 days, as was done in the experiments mentioned here. However, Japan has disassociated from this consensus, having approved new rules in March this year allowing the implantation of chimeric embryos in animal mothers, their gestation and subsequent birth (see [HERE https://www.observatoriobioetica.org/2019/08/japon-da-nuevos-pasos-en-la-investigacion-con-quimeras-humano-animales/31338](https://www.observatoriobioetica.org/2019/08/japon-da-nuevos-pasos-en-la-investigacion-con-quimeras-humano-animales/31338)).

#### **Embryo models: embryoids**

Continuing on with their research, Izpisua's group has now published an article in the journal *Cell* ([https://www.cell.com/cell/fulltext/S0092-8674\(19\)31080-3?\\_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867419310803%3Fshowall%3Dtrue#](https://www.cell.com/cell/fulltext/S0092-8674(19)31080-3?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867419310803%3Fshowall%3Dtrue#)), in which they describe a method for obtaining "blastoids" *in vitro*; these are embryonic structures in the blastocyst stage that can simulate the early stages of embryonic development *in vitro*. In this paper, it should be noted that the blastoids were obtained from stem cells derived from adult cells.

#### ***Bioethical Implications***

From a bioethical point of view, the possibility of obtaining *in vitro* models to study embryonic development, without having to use a real human embryo, is extremely attractive.

In the study ([https://www.cell.com/cell/fulltext/S0092-8674\(19\)31080-3?\\_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867419310803%3Fshowall%3Dtrue#](https://www.cell.com/cell/fulltext/S0092-8674(19)31080-3?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867419310803%3Fshowall%3Dtrue#)), some blastoids obtained were implanted in the uterus of mice, resulting in the generation of tissues — albeit disorganized — but never managed to produce a viable embryo. Nevertheless, the authors note that his work "pave[s] the way to creating viable synthetic embryos by using cultured cells".

From a bioethical point of view, we believe that the genetic differences that separate these embryoids from human embryos resulting from fertilization do not provide a well-defined boundary for consideration as humans or not, so their manipulation or destruction could lead to an attack on their intrinsic dignity if they are considered as individuals of the human species. Accordingly, we are of the opinion that the principle of bioethical prudence should be applied to this research. This recommends a moratorium until it can be clearly established whether or not these embryoids may be considered as human embryos and, consequently, that human lives are not being manipulated in these experiments.

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