Conselho
Nacional de
Ética para as
Ciências da Vida

# HUMAN EMBRYO MODELS

## RELEVANT ETHICAL ASPECTS

Position of the National Council of Ethics for the Life Sciences

**14 July 2023**

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## 1. Introduction

The international press recently announced that a research team from Cambridge University and the California Institute of Technology had produced a model incorrectly named a 'synthetic embryo', i.e., a structure similar to an embryo, formed not from fertilisation of an oocyte by a spermatozoon, but from stem cells, with the capacity to differentiate into various cell lineages. This was described as an 'innovative advance that avoids the need for ova or sperm'[1] and sparked a heated ethical debate in terms of the biological reality in question and its impact on human identity, in addition to how the research was described and disseminated.

In line with our mission of analysing the ethical problems brought to light by scientific progress in the fields of biology, medicine or health and life sciences, the National Council of Ethics for the Life Sciences (CNECV) deemed it necessary to succinctly clarify the scientific-technological reality in question, and above all to identify the main ethical issues it may give rise to, with the aim to contribute to the broad public debate called for by such a matter[2].

## 2. Background

A cursory glance at the research in this field over the past years enables us to quickly draw the conclusion that we are not in the presence of a new scientific breakthrough finding. This fact should not affect our ethical considerations, but instead highlight how astounding biotechnological advances are often developed without any public debate. The occasion should be used to encourage a serene, comprehensive reflection, without failing to question what was behind the announcement of the creation of the incorrectly named 'synthetic embryos'.

[1] 'Synthetic human embryos created in groundbreaking advance', as reported in *The Guardian* newspaper in its online version on 14 June 2023.
[2] Previous reflections by the CNECV on this issue: Opinion on Synthetic Biology (61/CNECV/2011); Opinion on Draft Law no. 126/X (Establishing the principles of scientific research on stem cells and the use of embryos) and Draft Law no. 376/X (Establishing the legal framework for the use of stem cells, for the purposes of research and the respective Therapeutic Applications) (53/CNECV/2007); Opinion on Human Cloning (48/CNECV/2006); Opinion on research on Stem Cells (47/CNECV/2005); Opinion on the Ethical Implications of Cloning (21/CNECV/97).

### 2.1. The origin of the announced research

In effect, the distant origin of what has been announced today goes back to the 1980s and 1990s (respectively in mice and in humans), when for the first time, so-called embryonic stem cells (ESCs) were isolated, from embryos in a pre-implantation phase (blastocyst stage). The ability to cultivate ESCs *in vitro* triggered a debate concerning the ethical implications of this kind of research, in addition when implying the destruction of the embryos. The Report of the Committee of Inquiry into Human Fertilisation and Embryology (Warnock Report)[3], presented to the British Parliament in 1984, established the '14-day rule'[4] in its ultimately liberal perspective, in Europe and beyond, thus restricting research using human embryos to that time limit.

### 2.2. Research lines and potential applications

ESCs can give rise to all the cells of the human body. Among their most relevant uses[5], of particular note is the modelling of the formation of human tissues *in vitro* that led to the field of regenerative medicine.

This area received another strong boost from the moment it became possible to create the first induced pluripotent stem cells (iPSCs), in 2006, for mice, and in 2007 for humans. iPSCs are formed by reprogramming techniques of adult cells, such as skin cells from any given individual, that are then transformed into 'embryonic-like' cells, from which any type of cells can be produced (e.g., cardiac cells, neurons, bone). iPSCs are, therefore, biologically equivalent to ESCs, except for their origin[6]. However, in contrast to the cells produced from ESCs, those produced from iPSCs are identical, from a genetic point of view, to those of the respective donors, and can be transplanted without risk of rejection. With

[3] Report of the Committee of Inquiry into Human Fertilisation and Embryology / Chairman: Dame Mary Warnock, DBE. Great Britain. Committee of Inquiry into Human Fertilisation and Embryology. 1984. Available at https://wellcomecollection.org/works/pxgeeqnf/items

[4] The '14-day rule' stipulates that experimentation on human embryos cannot allow them to develop beyond 14 days, or the appearance of the primitive/gastrulation line. Aach J, Lunshof J, Iyer E, M Church GM (2017) Addressing the ethical issues raised by synthetic human entities with embryo-like features. *eLife* 6:e20674

[5] Another example of how this technology is used is the fact it is one of the most robust methods to produce transgenic animals, which are essential for the discovery of new treatments for a wide range of pathologies.

[6] It is also pointed out that ESCs (and the biologically equivalent iPSCs) can give rise to all the adult human tissues, but ESCs were isolated from embryos where other cell types remained (which, for instance, give rise to the embryonic contribution to the placenta). It is not possible to create 'complete' embryos from these cell types; only to form body tissues (and amnio, for example).

this approach, regenerative medicine became more personalised, using cells from the individuals themselves to produce other cell types that could be clinically useful to them.

Recent research in this area, while not innovative, has tried to obtain all the cell types in a pre-implanted embryo from both ESCs and iPSCs through forced genetic alterations and/or manipulation of culture media. At least one of the four research groups working on this matter does not use any genetic alteration. As for the other ongoing research, it is not a question of the introduction of new genes, but rather of activating existing genes at specific moments. Joining the different cell types in the correct proportions leads to a spontaneous self-organisation, forming a structure that cannot be distinguished, from both the morphological point of view and gene expression, from embryos obtained through fertilisation. These constructs will also, theoretically, have an identical potential for development. However, none of these structures have been shown to fully develop and give rise to live births. As such, researchers have been careful to refer to them as 'embryo-like' structures, 'assembloids' or 'iblastoids', among other designations.

Given the present context, it is expected that regenerative medicine can eventually enable the replacement or re-establishment of damaged tissues and also, further in the future, lead to the production of synthetic organs. In addition to the benefits of this biotechnology within the scope of regenerative medicine, most researches in the area argue that a better knowledge of early embryonic development may help understand some causes of fertility problems, early miscarriages, and perhaps contribute to the analysis of embryo toxicology (both identifying possible toxic compounds and revealing their mechanisms of action), or the development of new treatments. Within this scope, this strategy can also contribute to the study of treatments of diseases, for example by testing gene editing tools. Models of genetically identical embryos, modified in different ways, may also be used to research how either genetic or environmental factors affect the development of the embryo, as well as to discover and test new medicines (Hyun *et al*, 2020)[7]. Rivron et al. (2018)[8]

[7] Hyun I, Munsie M, Pera MF, Rivron NC, Rossant J. Toward Guidelines for Research on Human Embryo Models Formed from Stem Cells. *Stem Cell Reports*. 2020 Feb 11;14(2):169-174. doi: 10.1016/j.stemcr.2019.12.008. Epub 2020 Jan 16. PMID: 31951813; PMCID: PMC7015820.

[8] Rivron N, Pera M, Rossant J, Martinez Arias A, Zernicka-Goetz M, Fu J, van den Brink S, Bredenoord A, Dondorp W, de Wert G, Hyun I, Munsie M, Isasi R. Debate ethics of embryo models from stem cells. *Nature*. 2018 Dec;564(7735):183-185. doi: 10.1038/d41586-018-07663-9. PMID: 30542177.

also stress the usefulness of these models in developing effective contraceptive strategies with fewer side effects.

### 2.3. Announcing the creation of 'synthetic embryos'

The dissemination of innovative research, that in fact is not groundbreaking in this case, was amplified by the general press based on information presented at a scientific conference by one of the four research teams who were working on the issue. The results were still in the pre-publication phase, and were presented without any reference to the other groups' work that was already publicly available at the time.

In an extraordinarily competitive area, which involves many powerful interests and requires substantial funding, being a pioneer is essential to maximize its external potential benefits. In this context, an exclusive announcement of preliminary conclusions can be explained by three lines of reasoning with differing ethical impacts. **(1)** A first reason is to establish precedence in the scientific-technological field. The researcher and his/her team will acquire a reputation for pioneering work that sets a benchmark, increasing the number of times it is cited, leading to enhanced prestige and widespread projection. In this case, the level of hyperbole around the facts will determine to what extent the scientific integrity of the work is violated. The benefits, however, go beyond the team in question, extending to its institution, with an impact in the assessment rankings and in the ability to attract financing, both public and private. **(2)** A second aspect to point out is the reporting of the preliminary results to peers, but above all to civil society, given the morally and socially controversial nature of the research, in this case by helping the public get accustomed to new methods of manipulating human life. To sum up, normalising the scientific-technological achievements consolidates the public conviction that these advances are unstoppable, and it is therefore not worth questioning them. **(3)** Finally, it is important to add that the invariable classification of biomedical developments as concrete therapeutic advances, albeit it is unproven and sometimes only projected, tends not only to legitimise the prosecution of this type of research, but also to remove the ethical issues it raises from the public debate. This imprudently ignores that new biotechnologies tend to begin in the therapeutic field and quickly move (through a process known as a 'slippery slope') towards a social utilisation for a range of purposes other than the original goals, which are not exempt of ethical problems.

The announcement of the creation of human embryo models requires ethical reflection and public debate, both to revisit 'classic' or persisting questions over the last three decades about research using human embryo-derived stem cells, which have led many national legal frameworks to adopt restrictions based on ethical values[9], as well as regarding the new challenges brought by the recent possibility of creating constructs or human (and, with different implications, other animal) embryo models (and, with different implications, embryo models for other species).

## 3. Specific ethical questions

The fact that biotechnological progress has enabled access to early human life, for both study and manipulation purposes, has always led to a four-fold question that remains unanswered: the biological reality in question, its ontological identity, its ethical categorisation and the consequent level of legal protection. In this light, the general recommendation calling for a duty of 'appropriate protection of the embryo' (Article 18(1) of the Convention on Human Rights and Biomedicine), in practical terms and in the absence of specific national regulations, leaves the action of the researchers largely unchecked.

### 3.1. 'Classic' or persisting ethical questions

The first and structural ethical question raised by research into human embryos or human embryo models is the **(1) legitimacy to manipulate human life,** which has acquired an ever-increasing number of variables and growing complexity. This question gives rise to a second one, which is crucial and relates to the **(2) legitimacy of the intentional destruction of embryos**. Both bring into question the **respect for the dignity of human life**, enunciating **arguments about the objectivation of embryonic life**, the **utility of inviable and/or surplus embryos for scientific experimentation** and appraising this possibility through the prism of the virtuousness of the purposes, and the underlying **added vulnerability and duty of protection**.

[9] A controversy that was at the root of the non-ratification and non-signing, by Germany and the UK for example, of the Convention on Human Rights and Biomedicine of the Council of Europe (especially Article 18(2), relative to prohibiting the creation of embryos for the purpose of research, in the case of the United Kingdom, and allowing research in 'supernumerary' embryos, in the case of Germany), and the respective Additional Protocols that have entered into Portuguese law, respectively, in 2001 and 2017.

**Hence research with human embryos, when permitted, shall always be exceptional, subsidiary and only justifiable if it can reasonably be expected to bring benefits for the prevention, diagnosis or treatment of embryos and other therapeutic purposes, requiring prior authorisation, on a case-by-case basis, by a competent authority.**

Additionally, it is generally forbidden to clone humans for reproductive purposes, to improve non-medical characteristics and to create chimeras or human-non-human hybrids (See, in Portugal, Law no. 32/2006 of 26 July, with amendments).

In parallel, **(3) the non-specificity of the expression 'other therapeutic purposes' may allow, under the pretence of a medical justification** – as mentioned previously – **unanticipated or unwanted practices**, which may be considered ethically reprehensible in light of the constant tension between the benefits of science for humanity and the respect for human dignity.

### 3.2. 'New' or emerging ethical questions

The name given to the cellular structure now produced (with the three cellular types that exist in a pre-implantation embryo) is not neutral. Indeed, it is infused with a strong ethical meaning. **(1) The 'synthetic human embryo' nomenclature may confuse the structures or constructs created in a laboratory with embryos generated through *in vitro* fertilisation (IVF).** The latter have the potential for development and live birth, which is yet to be proved in the case of the former (although in theory the potential for development is identical). In fact, it amounts to the production of cellular structures from stem cells that are similar to human embryos in their initial stages (human embryo-like structures), thus making **human embryo models' a preferable name**. This nomenclature is in line with the definitions of the International Society for Stem Cell Research (ISSCR). For these models, one must therefore also consider **(2) what ethical and legal protection statute should they be granted** and **(3) who will have the authority to approve this type of manipulation and research**, reviewing the ethical premises, the scientific merit and the possible therapeutic application of each research project. **(4) It is also necessary to reflect on the 14-day rule for the development of the embryo as the limit for research purposes**, as the criterion may have to be linked to the complexity of its biological architecture instead. **There is, therefore, a need to reflect on, and possibly review the legal**

**regulations in force on this matter, namely the Portuguese legislation.**

It has also become obvious that **(5) the true innovation in question is not a scientific or technological matter, but an ethical one**, brought to light by the new challenges involved in the process of creating these cell-based structures and their possible developmental capability.

On this issue, it is worth highlighting at least three important ethical questions, which are broad in scope and can, in the long-term, forecast the roadmap along which the research in these models is heading.

The first one concerns the **(6) potential creation of *in vitro* human foetuses, aimed at shortening, at least, or in the long-term even suppressing uterine gestation.** Experimentation in ex-utero embryogenesis in animals has been carried out for many years, as has the creation of possible artificial uteri. Simultaneously, the viability threshold for ex-utero human foetuses has been decreasing in time, thus reducing the possible length of pregnancy. Meanwhile, several arguments continue to be put forward supporting ex-utero gestation, starting with therapeutic reasons (e.g., the risk some women run during pregnancy and when giving birth) and quickly moving onto social aspects (e.g., convenience for a woman's professional career).

This leads to a second ethical question arising from to the future possibility of generating children from the somatic cells (e.g., skin cells) of an adult individual: **(7) the use of an individual's own iPSC cells may produce a theoretically identical artificial embryo** of this same person, which would be a new potential avenue to human cloning. **This would imply the return of past arguments in support of human cloning, which has meanwhile been banned internationally.**

Travelling down this path, the current utopic possibilities are not necessarily reassuring, as the use of iPSCs for human reproduction would allow **(8) the generation of a parentless child in a new rendering of the concept of 'being orphan' – a radical and absolute orphanhood.**

In any of these three pathways made possible by the production of human embryo models from stem cells, which theoretically have the potential for full development, more than the aspect of physical integrity it is important to analyse **(9) the psychological impact of these new generation and gestation conditions on the new being, on his/her individual identity as a being of relation, on the development of his/her personality** based on his/her life story and genetic origins, on

his/her sense of belonging to a community and development of a sense of solidarity.

## 4. Conclusion

Putting into context the progress of science and the new technologies, it is possible to immediately arrive at some **fundamental ethical consensuses** on the scientific data noted here, such as the need for integrity, transparency and clear and truthful communication, namely regarding its applications, but also relative to its potential risks and threats. Civil society should also be clearly informed and made aware of science, its activity and what it entails, as should the political decision makers, encouraging forums of dialogue and democratic participation.

In this intersection between ethics, law and politics, the CNECV shall continue to carry out its competencies and responsibilities to analyse, raise awareness and follow-up on the ethical issues involved in this matter, which may in the future justify a more in-depth pronouncement about the application, both current and potential, of research using human embryo models, as a prior and necessary moment for a possible review of the applicable legal framework and governance procedures.

Lisbon, 14 July 2023.
The President, Maria do Céu Patrão Neves.

Rapporteurs: Maria do Céu Patrão Neves, President, João-Ramalho Santos, Council Member, and Cíntia Águas, Executive Secretary.

This position statement was approved unanimously on 14 July 2023, at the 279th Plenary Meeting of the CNECV, which was attended by the following Council Members: Maria do Céu Patrão Neves, President; André Dias Pereira, Vice-President; Carlos Maurício Barbosa; Helder Mota Filipe; Inês Fronteira; Inês Godinho; João Queiroz e Melo; João Ramalho-Santos; José Manuel Pereira de Almeida; Luís Madeira; Margarida Silvestre; Lurdes Martins; Miguel Guimarães; Paula Pinto de Freitas; Pedro Fevereiro; Rosalvo Almeida; Sandra Horta e Silva.