Saint-Denis, September 21, 2023

Opinion of the Conseil d'orientation : stem cell-based embryo models

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This document is a translation. The original French version drawn up by the Conseil d'orientation is the only official version.

Context

In France, human embryo research is currently subject to an authorisation framework with an opinion from an ethics committee, the Conseil d'orientation, which must evaluate several criteria, in particular: (i) the scientific relevance of the protocol, (ii) the existence of a medical purpose, (iii) the absence of an alternative to the use of human embryos, and (iv) compliance with fundamental ethical principles. Since the French Bioethics Act of August 2, 2021, research protocols involving human embryonic stem cells (hESCs) or induced pluripotent stem cells (hiPS) for certain purposes defined by law must be notified to the Agence de la biomédecine, which must obtain the opinion of the Conseil d'orientation. Research protocols involving hESCs or hiPS cells for the purpose of "obtaining *in vitro* stem cell-based embryo models" also known as "embryoids," are covered by this provision.

The development of such stem cell-based embryo models is recent. The first publications in this field date back to 2014 (1); in recent years, progress has accelerated with the publication of mouse and human embryo models (2–4).

Since the beginning of 2023, the Conseil d'orientation has already issued an opinion on protocols involving human embryoids.

It therefore seemed necessary to ask and attempt to answer certain questions. The following is a non-exhaustive list, mentioned in broad terms several years ago by a group of researchers (5):

- Should embryo models now or in the future be treated legally and ethically as human embryos, and according to what criteria?
- What research applications with human embryo models are ethically unacceptable *a priori*?
- Should a developmental limit be set for human embryo models?
- Should information forms for couples wishing to donate their embryos for research be revised to reflect these new areas of research?
- Should specific consent be required from individuals who have donated somatic cells for the creation of iPS cells that can be used to generate human embryoids?

In this preamble, the Conseil d'orientation emphasises that the thoughts and opinions that can be expressed today are valid only in light of the current state of knowledge and will probably no longer be valid tomorrow. Our thinking will have to evolve as technology develops.

Scientific background

Terminology: the International Society for Stem Cell Research (ISSCR) prefers the term "stem cell-based embryo models" to the term "synthetic embryo" that is sometimes used (6, 7). The equivalent term is "embryoid," which is the primary term used in this text.

Since the early days of *in vitro* fertilisation and until recently, the culture period for human embryos was technically limited to 7 days post fertilisation; however, in 2016, the development of protocols made it possible to extend this period to 12 to 13 days (8–10). However, embryos cultured under these conditions became increasingly disorganised and did not reflect the developmental stage of a 13-day embryo. Nevertheless, protocols are constantly being improved, particularly through experiments using monkey embryos (11).

Embryoids or embryonic models are obtained from the three-dimensional self-organisation of hESCs or hiPS cells, which may or may not be supplemented with stem cells reflecting extra-embryonic tissues. Stem cell-based embryo models can therefore be generated with varying degrees of completeness and reflecting different stages of development. Some models mimic development at the gastrulation stage (consisting of the establishment of the mesoderm, the third layer of the vertebrate disc, which in humans begins around day 15 of embryonic development). These models have been developed in mice (12–14) and in humans (15–17): they are commonly referred to as «gastruloids». These structures are incomplete compared with natural embryos at the same stage, lacking the anterior part of the body (from which the head and brain will later form) and the extraembryonic appendages, particularly the trophoblast, the cell line that forms the placenta (15). In other mouse models, ESCs are aggregated in combination with stem cells reflecting the extraembryonic tissues normally destined to form the placenta and yolk sac (18). These mouse models have demonstrated the ability to develop to a stage corresponding to approximately one-third of gestation (19, 20). Other models have allowed reconstruction of a complete model of the murine (21–24) and human embryo before or after implantation by aggregation of hESCs and hiPSCs capable of forming cells reflecting the embryo and its appendages (25–30). These models are generally referred to as "blastoids," in reference to the "blastocyst," which characterises the stage of the human embryo between the 5th and 6th day of development. In mice, these blastoids are capable of implanting in the endometrium with a frequency of 20% (31) , but they become disorganised *in vivo* and no fetus has yet formed. Regarding terminology, these models (blastoids, gastruloids, etc.) represent different embryoids, which is a generic term.

Scientists consider that there are two different types of embryo models (32):

- Non-integrated models: at the current state of knowledge, it is assumed that these models will never be able to form a complete embryo, even if protocols are improved, because they lack certain embryonic and/or extraembryonic tissues.
- Integrated models: they can reconstitute the entire embryo and at least part of the different extraembryonic appendages (trophoblast and primitive endoderm). Therefore, at the current state of knowledge, it is assumed that these models, after improvement of the protocols, could acquire the ability to form a fetus or even a newborn. When complete (blastoids), these integrated models can implant into a uterus (in mice) or into layers of endometrial cells (in humans), initiating development after implantation.

International legislation

At the European level, few countries intend to adopt specific legislation on embryo models, with the exception of the Netherlands (the *Embryo Act*, currently being drafted, raises the question of the legal definition of embryos and embryoids and aims to define the limits of culture time). Most countries refer to the ethical guidelines issued by the ISSCR, which are a reference for researchers around the world, especially in countries where research on embryos and hESC is not regulated by law. The latest edition of the ISSCR Ethical Guidelines (6) states that, based on the current state of science, models should not be considered embryos from either a biological or legal perspective. The ISSCR distinguishes three categories of research: those that do not raise ethical issues, those that require vigilance, and those that should be prohibited. In the latest edition of the ISSCR ethical guidelines, both types of embryo models (integrated and non-integrated) are considered to suggest a gradation of ethical concerns. According to the ISSCR, research using integrated models must be approved by ethics committees, while research using non-integrated models need only be notified to the same committees. The ethical guidelines also include the transfer of embryoids with human stem cells into uteri, whether human or animal, or their combination with uterine explants, in the category of "prohibited research." However, because embryoids are formed from stem cells and do not require the destruction of embryos, they are often presented as an ethical alternative to using embryos for research.

The question of limits in the culture of human embryos is not new. In the United Kingdom, the Human Fertilisation Embryology Authority (HFEA) took a position on this issue in 1984, designating embryos of less than 14 days as "pre-embryos" (a terminology that has since been abandoned), based on the conclusions of the report of the committee chaired by Mary Warnock (1984). At that time, UK legislation classified as criminal the continuation of research on an embryo beyond the 14th day of development, anticipating the future, because at that time no team could culture human embryos beyond 7 days, which corresponds to the stage of hatching of the blastocyst outside its zona pellucida. Recently, the latest edition of the ISSCR ethical guidelines lifted the ban on culturing human embryos beyond 14 days and referred research teams to their national jurisdictions. Nevertheless, there is still some consensus in favor of maintaining the 14-day rule, as about fifteen countries have included it in their laws (including France in the Bioethics Act of August 2, 2021) or in their national guidelines. However, it should be noted that in the United Kingdom and the Netherlands, discussions are at an advanced stage and in favour of an extension, and that in the United States, authorisation has already been given in the state of New York to cultivate embryos beyond this limit. Similarly, in Asia (China, Japan), the perception of the embryo differs from that of many countries, especially in Europe, and an extension of embryo culture beyond the 14-day period could be envisaged from a sociocultural point of view.

Setting a limit is always arbitrary, but the 14-day rule is based on two embryological events: (i) On the 15th day, the primitive streak appears in the epiblast (one of the layers of the embryonic disc), leading to gastrulation (formation of the mesoderm, the third layer of the disc) and, a few days later, to the appearance of the neural plate (precursor of nervous tissue). (ii) Day 14 marks the limit beyond which the embryo can no longer split to give monozygotic twins. As mentioned above, this 14-day limit does not apply to embryoids, for which there is no culture limit in France under current legislation. At the international level, most countries consider that their regulatory framework should be identical to that for hESC, which precludes setting an *a priori* time limit for culture. Only Australia considers embryoid research in the same way as embryo research and has a stricter framework.

What ethical considerations must be taken into account?

First, the question of the scientific interest of research in this area must be asked. The answer is positive, because these embryoids open for the first time the possibility to know and better understand the early development of the human embryo. The period between the end of the second week and the beginning of the second month is called the "black box," after which research can be carried out using embryos from terminated pregnancies. A wide range of biomedical applications can be envisioned: more efficient techniques for medically assisted reproduction; pharmacological and toxicological testing; better understanding of developmental abnormalities and pregnancy losses with the possibility of developing preventive treatments; development of cell therapies, etc..(33). In addition, as mentioned above, these embryoids represent an interesting alternative from an ethical point of view because, as models and as long as they are not considered as embryos, they allow researchers to avoid experimentation on human embryos that will be destroyed at the end of the research.

The "status" of embryoids can be considered in several ways:

- 1. restrictive position : embryoids are not embryos, but techniques will improve and the goal is to achieve equivalence. Consequently, research on embryoids should already be regulated in the same way as research on embryos.
- 2. permissive position : embryoids are not embryos, they are cultured cells. No special framework should be provided, but the same rules should apply as for all research on cell lines.
- 3. intermediate position : embryoids are not embryos, but they model early embryonic development and enable scientific and medical advances. Therefore, they deserve a specific framework that should be more flexible than that for embryo research, but more stringent than that for research on traditional cell lines.

This intermediate position is supported by many embryologists and scientific societies, including the ISSCR. It is also the position adopted by the Conseil d'orientation.

It is interesting to note that all three positions share a common assertion : **To date, embryoids should not be considered as embryos**. At present, the distinction is easy to make because these embryoids cannot lead to full development in mice (22, 24, 31). However, it is likely that, given the rapid scientific progress in this field, animal embryoids will acquire properties in the near future that will no longer allow them to be distinguished from naturally conceived embryos (Turing test*[1] passed).

[1] named after a mathematician who, in 1950, defined criteria for distinguishing between computer-generated artificial intelligence and human thinking.

The Conseil d'orientation agrees that even if this situation were reached in the future, human embryoids could not essentially be equated with embryos for two reasons:

- The **origin** of the formation of these structures : these models arise from stem cells (ESC or iPS) and not from a natural conception leading to the formation of a zygote after a fertilization process consisting of the union of two haploid genomes, each carried by the parental gametes. It should also be noted that this is not a cloning technique, which is recognised and prohibited by French law as a means of creating human embryos.

- **Intentionality** : natural embryos are initially part of a parental project, even if they are embryos donated for research. This intentionality is not present in the case of embryoids. One might object that once an embryo is donated to research, it is no longer part of a parental project anymore, and thus loses its status as « a person in the making », which is the status defined by the Comité consultatif national d'éthique (CCNE - the French national ethical board)(34); however, there was indeed an initial parental project: the procreation of a child.

The parallel that is constantly drawn between embryoids and embryos forces us to question the **status of the human embryo.**

This question has been asked for a long time, without a satisfactory answer being found so far, because it raises a fundamental question: At what point can the embryo be considered as a human person? The answers vary widely, depending on culture, religious position, etc. Among the many existing points of view, three can be mentioned:

- the embryo must be considered as a human person from the moment of conception.
- the status of the embryo depends on its stage of development.
- the status of the embryo depends on the parental project: the embryo is considered « a person in the making » as long as it is part of such a project. It should be noted that the French legislation goes in this direction, since an embryo can be destroyed or donated for research when it is no longer the object of a parental project, as expressed by progenitors.

From a biological perspective, it can be said that the zygote (the product of fertilisation) has all the biological potential to develop into an embryo, which then becomes a fetus at the end of the 8th week (when organogenesis is considered to be largely complete), which then develops until birth. Development, from zygote to birth, is thus a continuum, with any segmentation being artificial.

In one of its first opinions, the CCNE defined the embryo as a «potential human person»(34); however, in a more recent opinion, it argues that it is impossible to define a status for the embryo (35).

What ethical criteria should be applied to the regulation of embryoids? In addition to the basic ethical principles to be taken into account according to the political philosophies on which societies are based, the Conseil d'orientation takes up several principles also established by the ISSCR that seem important to consider:

The **principle of proportionality** requires an assessment of the "risk-benefit" balance in relation to the objectives of the proposed research.

The **principle of subsidiarity** requires that the means used be strictly necessary to achieve the intended objectives.

The **precautionary principle** requires that, in the absence of duly established scientific knowledge, the adoption of effective and proportionate measures be taken to prevent serious and irreversible harm.

The scientific interest of this research has been described above, including the scientific relevance between the second week and the second month of development, the presence of medical purposes, and the absence of experimental alternatives. The risks associated with culturing these models are more difficult to assess, but it can be considered that, given the current state of science, the more advanced the development of the model in culture, the more these models can be expected to deviate from the physiological development of the embryo (26, 29). However, when this deviation becomes too great, the model loses its relevance and its scientific and medical utility. Requests for approval to cultivate models for a specific developmental period must therefore be discussed on the basis of the relevance of the model during that period. Consequently, the extension of a model's culture period must be justified by its ability to faithfully and effectively model the biological period under investigation.

The principle of subsidiarity implies that a question should be addressed and resolved by the means most appropriate to the ends sought. For example, if the goal of the research is to explore the mechanisms involved in cardiac morphogenesis, then it should be conducted on the minimum structure necessary to answer the question : a cardiac organoid, not an embryoid.

The question of consent for research must be raised, considering the possibility of updating the forms that provide the most accurate information to couples or single women who wish to donate their embryos for research, as well as to individuals who donate somatic cells with the aim of creating iPS; because embryoids can be formed from two cell sources:

- hESC: derived from the inner cell mass of a blastocyst
- hiPS cells : obtained from the somatic cells of a person

Conclusions

The spectacular scientific advances made in recent years in the field of embryogenesis suggest that in the near future these embryoids may acquire properties that would put them on a par with natural embryos and allow them to give birth to viable animals. Currently, there is an international consensus against the transfer of human embryoids into a human or animal uterus (6, 32). The Conseil d'orientation considers that embryoids enable scientific and medical advances that justify their use in fundamental and applied research. However, the Conseil d'orientation emphasises the risks of misuse and the need to introduce regulations to prevent any risk of unethical behavior.

The Conseil d'orientation considers that **human embryoids cannot, in essence, be equivalent to embryos** for two reasons:

- **The origin** of the formation of these structures : they arise from stem cells (hESC or hiPS) and not from natural conception, i.e., a fertilisation process consisting in the union of two haploid genomes, each carried by the parental gametes.

- **Intentionality**: embryos are conceived as part of an original parental project, even if they are embryos donated for research, which is not the case for embryoids.

The opinion of the Conseil d'orientation focuses on embryoids, but prompts it to formulate an opinion on the duration of culture of human embryos, for which the current French law sets a limit of 14 days. The Conseil d'orientation is not in favor of extending this period, even if scientific progress would make it possible, since researchers also have the possibility of studying embryoids that can be cultured for a longer period. **It is proposed that research on integrated embryoids, especially the most complete ones (e.g., blastoids), be permitted up to a stage equivalent to the 28th day of development of the natural embryo, with a complete cessation of all experimentation beyond that stage.** Such research will make it possible to significantly shorten the "black box" period, which currently extends from day 14 to the beginning of the second month of development. There is no justification for culturing these integrated models beyond 28 days because, at the current state of science, these models deviate from physiological development and therefore lose their scientific and medical relevance and usefulness. Moreover, after the first month, there are alternative models that, in accordance with the principle of subsidiarity, make the use of these models unnecessary. For example, incomplete (e.g., non-integrated) embryonic models that focus on the development of an organ or set of organs can be used.

The risks of prolonging embryoid culture to the 28-day stage might also be considered. Apart from the scientific interest already mentioned, it should be noted that this stage corresponds only to the beginning of organogenesis. The brain is at the three vesicle stage and the cerebral cortex develops later. It is difficult to determine the time of onset of pain sensation or even consciousness, but current data place it beyond the 20th week, more likely around the 24th week.

These considerations, however, do not preclude the need for correspondingly greater vigilance in protocols that involve experimentation on embryoids beyond 14 days of culture, with researchers having to justify such an extension on a case-by-case basis.

The Conseil d'orientation considers that the risks of commercial exploitation of embryoids and their derivatives (cells, tissues, or organs) should be a point of vigilance. Human embryoids may only be used for scientific research purposes. In accordance with ISSCR recommendations, ***in vivo*** **implantation should not be allowed.**

Regarding the legal framework of these embryo models, the Conseil d'orientation proposes that the legislator considers this research in a third specific way, between that for hiPS or hESCs, which would be too permissive, and that for embryos, which would be too restrictive.

Finally, **the issue of consent to research needs to be reconsidered** to update the information and consent forms that couples or single women who wish to donate their embryos for research, or individuals who wish to donate somatic cells to create iPS cells, receive and sign.

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Abbreviations

CCNE : Comité consultatif national d'éthique

(h) ESC : (human) embryonic stem cells

HFEA : Human fertilisation and embryology authority

(h) iPS : (human) induced pluripotent stem cells

ISSCR : International society for stem cell research