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# The moral status of human embryo-like structures: potentiality matters?

*The moral status of human synthetic embryos*

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Research in early human development has undergone rapid progress during the past years, not least owing to two new methods for the *in vitro* culture of human embryos and for the generation of embryo-like structures. However, these very methods raise new ethical issues regarding the creation and use of human embryo-like structures, the moral status of which is uncertain. In particular, they raise questions about the moral significance of the potential of such embryo-like structures to develop into a human fetus and a mature human being. This potential to develop into human beings is one of the major points of contention in the ethical debate regarding human embryonic stem cell research and whether it is morally acceptable to destroy human embryos for research. We shall address the question of how consistency demands a comparable argument for human embryo-like structures and discuss the implications for future research in human embryonic development.

## Current status of research in human development

In 2016, two research groups, Magdalena Zernicka-Goetz *et al* from the University of Cambridge in the UK, and Ali Brivanlou *et al* from Rockefeller University in the United States, developed *in vitro* culture methods to grow human embryos outside the body beyond the implantation stages. In 2019, Weizhi Ji, Tianqing Li, *et al* established a three-dimensional culture system for human embryos. These methods now allow researchers to observe the developmental process of early human embryos *in vitro* and to subject it to far more detailed analysis than has previously been possible. Thus far, embryos have only been cultured for 12–13 days after fertilization, in accordance with the widely observed 14-day limit for research involving human embryos.

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In parallel, researchers have also successfully created embryo-like structures from pluripotent stem cells (PSCs) such as embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). In 2014, Zernicka-Goetz's and Alfonso Martinez Arias's research groups produced embryo-like structures at the gastrulation stage from mouse ESCs and Eric Siggia and Brivanlou's teams generated such structures from human ESCs. These embryo-like structures differ from normal embryos in terms of their structure and morphology. Although they undergo many of the morphological and pattern formation events of early embryos, they do not undergo all of the same events. More specifically, they are constituted by aggregates of pluripotent cells, which form only a partial structure of normal embryos.

Using these techniques, researchers have reported novel insights on embryo-like structure and human organizer cells. With respect to the former, scientists developed a culture system for embryos using an extracellular matrix (ECM) and generated an embryo-like structure using mouse stem cells. In 2018, Nicolas Rivron's group created an embryo-like structure similar to a blastocyst—they named it a "Blastoid"—by assembling mouse ESCs and trophoblast stem cells (TSCs). As a result of transferring and testing the embryo-like structure *in utero*, an implantation-like response on the uterine wall was observed although it subsequently stopped developing. These results suggest that embryo-like structures produced from human PSCs will be a promising experimental system to explore post-implantation embryonic development. It might also have further clinical applications in infertility treatment and transplantation using organoids in the future.

Researchers have also transplanted human organizer cells into non-human animal embryos. These organizer cells play a central role in early human development, and the primitive streak—the beginning of gastrulation and the formation of the three germ layers—emerges from them. In 2018, Brivanlou's research group experimented

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with transplanting human ESC-derived organizer cells into chick embryos: chick nervous tissues were formed, while human organizer cells promoted chick cells to differentiate. The potential of human ESC-derived organizer cells to induce a secondary axis in chick embryos has also been shown, though the follow-up observation of this study was only 48 h after transplantation. The study implies that the transplanted human organizer cells play an essential role in the appearance of the primitive streak. By performing studies in which researchers continuously transplant organizer cells into non-human animal embryos and analyze their development, we may substantially increase our understanding of the role of human organizer cells in early embryogenesis and gestation.

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Studies using human organizer cells also allow observation and analysis of the primitive streak *in vitro*, in co-culture with human PSCs (Table 1). Notably, during embryonic development, the three-dimensional location of cells is essential. Each cell has its own specific position and plays a particular role to generate the correct tissues. This positional information is provided by concentration gradients of various signaling molecules. Cells differentiate, proliferate, and migrate based on this three-dimensional positional information. To obtain a detailed understanding of human development, it is therefore essential to create a three-dimensional structure close to actual embryos. Such three-dimensional experimental systems are being developed, but more refined methods would help to elucidate the "black box" of human development.

## Do embryo-like structures have moral status?

Although these new methods hold great promise for research, they also raise an ethical question: how should we understand the moral status of these human embryo-like structures? In the ethical debate about research into embryonic development, one of the major issues has been the question whether it is morally acceptable to destroy human embryos with the potential to develop into human beings. The creation of embryo-like structures complicates the situation. The reason for this is that embryo-like structures produced using human PSCs *in vitro* might have the potential to become mature human beings. Yet, even if the currently produced human embryo-like structures are transplanted into the uterus, there is no guarantee that normal embryonic development would occur—indeed, for the moment, at least, there is no good reason to transplant embryo-like structures in this way. However, some have argued that it is possible to create embryo-like structures that would be closer to intact embryos in this regard (Denker, 2014).

There has already been some discussion regarding the moral status of embryo-like structures (Pera *et al*, 2015). Insoo Hyun argues that we should refrain from creating intact embryos from human PSCs, since there is no real scientific necessity for doing so (Hyun, 2017). However, in order to comprehensively understand human development, it may be necessary to analyze embryonic development in detail in comparison with normal embryos. It is likely that experimental systems using mouse embryo-like structures will serve as a precedent to proceed with similar research using human embryo-like structures. If mouse embryo-like structures are transplanted into the uterus and develop to term, then we might predict that the same results could be obtained in humans. Currently, if human embryo-like structures were developed in a way that led to a primitive streak, it is unclear whether it would be permissible to continue the research; or indeed whether it is permissible to generate human embryo-like structures that would avoid the appearance of a primitive streak.

It is crucial to point out that embryo-like structures can be quite different to normal human embryos. In acknowledgment of this, Aach *et al* (2017) termed what we call embryo-like structures as "synthetic human entities with embryo-like feature (SHEEFs)". However, despite these differences, if these embryo-like structures have the potential to develop into fetuses and mature human beings, then we will have to confront the question of their moral status, since such potential is often understood to undergird the moral status of normal human embryos.

*"... if these embryo-like structures have the potential to develop into fetuses and mature human beings, then we will have to confront the question of their moral status ..."*

Contrary to Hyun's claim, we assume that the creation and use of these embryo-like structures will become necessary to acquire useful scientific knowledge. Here, we assume that so-called *complete* embryo-like structures derived from PSCs are entities that have every component that a normal human embryo has. These components include the cells that will constitute the fetus but not extraembryonic material; "the embryo proper". In addition, a complete embryo-like structure would also include cells that develop into crucial extraembryonic material, including a hypoblast (also called a primitive endoderm, which forms the yolk sac and contributes to the formation of the placenta) and a trophoblast (which becomes the placenta). Notably though, existing embryo-like structures are not complete in this way, because they lack both the hypoblast and trophoblast. If this is the case, there is a pressing moral question in this context: how should we consider the potential of complete or incomplete human embryo-like structures in comparison to intact embryos?

## Potential matters

Moral status arguments based on potential must appeal to both an empirical claim and an ethical claim. The empirical claim is that "entity x has the potential to develop into y". The moral claim is that the potential described in the empirical claim confers greater moral status on x, than x would have had in the absence of this potential. Of course, even if embryo-like structures have some degree of potential, one may yet deny that this potential is in any way relevant to moral status. Alternatively, one might argue that the potential of embryo-like structures is only sufficient for low degrees of moral status. Indeed, many countries that regulate

**Table 1. Types of embryo-like structures.**

| Models | Original components | Species | Features | References |
|---|---|---|---|---|
| Blastoid | ESCs + TSCs | Mouse | Decidualization *in utero* after implantation<br>Similar morphology and gene expression to blastocysts | Rivron *et al* (2018) |
| ETX-embryoid | ESCs + TSCs + XENCs | Mouse | Similar morphology to E5.5–7.0 post-implantation mouse embryos<br>Induction of anterior visceral endoderm, definitive endoderm, mesoderm<br>Showing anterior–posterior patterning, gastrulation | Sozen *et al* (2018)<br>Zhang *et al* (2019) |
| Micropatterned stem cell culture | ESCs | Human | Patterned cell fates by WNT, BMP, and activin/NODAL signaling in 2D culture<br>Induction of three germ layers, trophectoderm, and organizer | Warmflash *et al* (2014)<br>Martyn *et al* (2018) |
| Epiblast-amniotic sac structure | ESCs | Human | Formation of the pro-amniotic cavity and an asymmetric amniotic ectoderm-epiblast pattern<br>Specification of primordial germ cells and primitive streak cells<br>Showing gastrulation | Shao *et al* (2017)<br>Zheng *et al* (2019) |
| Gastruloid | ESCs | Mouse | Showing antero-posterior, dorso-ventral, left–right axes and somitogenesis<br>Post-gastrulation stage structure lacking brain and heart | van den Brink *et al* (2014)<br>Beccari *et al* (2018)<br>van den Brink *et al* (2020) |

XENCs, extraembryonic endoderm cells; TSCs, trophoblast stem cells.

the research use of human embryos implicitly endorse a similar view regarding ordinary embryos, according to which moral status gradually increases from conception to birth, or some point before birth. Such regulations treat the potential to develop into a mature human being as a basis for some degree of moral status, even if it may still be permissible to use these entities in research. So what degree of moral status should different kinds or degrees of potential to develop into a mature human being confer?

The case of somatic cells demonstrates that not all forms of potential are morally relevant. Although at least some human somatic cells have the potential to develop into mature humans when using somatic cell nuclear transfer (SCNT), it would be absurd to conclude that all somatic cells have significant moral status based on said potential.

However, even if the potential of a skin cell is not sufficient for significant moral status, there are other forms of potential that can be morally relevant. One can distinguish between "active potential"—whereby an entity's development into a mature human is determined by internal factors—and "passive potential" when development into a mature human being is dependent upon at least one external factor, such as being placed into the appropriate environment (Strong, 2006). Based on this distinction, *in utero* embryos would have active potential, while *in vitro* embryos (and skin cells for that matter) have only passive potential. It could then be argued that active potential is sufficient for moral status, but passive potential is not.

But it is not clear that this distinction between active and passive potential is a convincing basis for claiming that embryo-like structures have moral status. Here, we need to distinguish between different forms of passive potential, namely advanced passive potential (where development of the entity into a mature, fully formed human is dependent upon it being placed into the right environment *and* where significant transformation is *not* required) and basic passive potential (where development of the entity into a mature, fully formed human is dependent on the entity being placed into the right environment *and* significant transformation). On this understanding, some countries attribute moral status to *in vitro* embryos on the basis of their advanced passive potentiality given that they contain the inner cell mass (ICM) that develops into the fetus and the trophoblast that becomes the placenta when they are placed in a womb. If this is so, complete human embryo-like structures which are structurally and morphologically equivalent to intact human embryos could also be said to have the same kind of potential.

In contrast, this understanding of the moral relevance of potential is not straightforwardly applicable to embryos with a defective trophoblast. Such embryos would not be regarded as having the same kind of morally significant potential, because they possess only *basic* passive potential: They would require significant transformation to develop into a mature human being. Yet, a defective trophoblast in such an embryo could be replaced with a healthy trophoblast and a couple undergoing *in vitro* fertilization could bring that embryo to term (Devolder, 2009). To say then that such embryos lack morally significant potential appears counterintuitive; basic passive potential may thus matter morally to some extent

Thus, one could argue that embryos containing the ICM, being in the Aristotelian "final form" of the human, have morally significant potential because they have all the genetic material necessary to develop into a mature human if two criteria are met: The technology for trophoblast replacement exists; and there is intention to use the technology. Notably, if ICM cells are morally relevant, then even PSCs could have the same capacity to develop into a mature human being by using tetraploid complementation (Sawai, 2014). This suggests that entities which are equivalent to the embryo proper but which lack a

**Table 2. Degrees of potential of types of cells.**

| Type of potential | Active potential[a] | Passive potential | | |
|---|---|---|---|---|
| | | Advanced passive potential[b] | | Basic passive potential[c] (entities which are not equivalent to the embryo proper) |
| | | Category A (entities which have every component such as embryo proper and which have hypoblast and trophoblast) | Category B (entities which are equivalent to embryo proper, but which lack hypoblast and trophoblast) | |
| Type of cells | *In utero* embryos | *In vitro* embryos, PSC-derived complete embryo-like structures | ICM cells, PSCs, PSC-derived incomplete embryo-like structures (e.g., micropatterned stem cell cultures, epiblast-amniotic sac structures) | Somatic cells, PSC-derived incomplete embryo-like structures (e.g., gastruloids) |

[a]Development into a mature human is determined by internal factors.
[b]Development of the entity into a mature, fully formed human is dependent upon it being placed into the right environment and where significant transformation is not required.
[c]Development of the entity into a mature, fully formed human is dependent on the entity being placed into the right environment and undergoing significant transformation.

hypoblast or trophoblast may still have advanced passive potential. Some types of PSC-derived incomplete embryo-like structures, such as micropatterned stem cell cultures or epiblast-amniotic sac structures), are indeed equivalent to the embryo proper and would have advanced passive potential, while other, incomplete structures such as gastruloids are no longer equivalent to the embryo proper. Since ICM cells, PSCs, and some PSC-derived incomplete embryo-like structures have advanced passive potentiality, it would be consistent that they are treated equally, though we further divide their potentiality into two categories (Table 2).

*"The 14-day limit was "meant to be a solution of compromise rather than a means to find the most consistent moral view"..."*

To sum up, based on our distinction of degrees of potential to develop into a mature human being, only *in utero* embryos have "active potential", while anything else from somatic cells to *in vitro* embryos have "passive potential". A further distinction between degrees of passive potential suggests that *in vitro* embryos and PSC-derived complete embryo-like structures have advanced passive potential, whereas somatic cells, ICM cells, and PSCs have only basic passive potential. In our view, ICM cells, PSCs, and some types of PSC-derived incomplete embryo-like structures also have advanced passive potential since they have all the genetic material necessary to generate a life in a single entity, while somatic cells and some other types of PSC-derived incomplete embryo-like structures only have basic passive potential. The same degree of potentiality requires equal moral consideration, although it is not yet clear that considerations of potentiality will be sufficient for ethical limitations on research using human embryo-like structures.

## Implications for research

Many countries currently allow, under certain conditions, the research use of human embryos but only within 14 days of fertilization to respect the "special value" of human embryos. Research on embryos prior to this limit is partly justified on the basis that these embryos lack sentience and that it is still possible for the embryo to divide into two separate individuals, a process known as "twinning".

As Giulia Cavaliere emphasized in her discussion of the UK Warnock report that recommended the 14-day limit, the committee was organized for ensuring public trust in and as an external oversight of scientific research. The 14-day limit was "meant to be a solution of compromise rather than a means to find the most consistent moral view" (Cavaliere, 2017). At the time, it was not technically possible to cultivate embryos *in vitro* beyond the blastocyst stage, and any longer period limit for maintaining human embryos *in vitro* was "a purely hypothetical limit". This moral and scientific compromise has been appreciated politically and has been enacted in the UK, the United States, Japan, and many other countries so far (Hyun, 2017).

However, as discussed above, current *in vitro* culture methods could be used to grow human embryos and embryo-like structures beyond 14 days after fertilization or the appearance of the primitive streak. For that reason, it is currently debated whether the 14-day rule is still justified, and whether it would be appropriate to extend the time limit in light of the new technical possibility of culturing embryos and embryo-like structures (Cavaliere, 2017; Appleby & Bredenoord, 2018).

*"As many countries have based their regulation of research using human embryos on the potential to develop into a human being, we will need to include the degrees of potential of human embryo-like structures for moral consideration."*

Recently, the International Society for Stem Cell Research (ISSCR) published recommendations for oversight of research using human embryo-like structures (Hyun *et al*, 2020), in which they distinguish embryo-like structures in two categories: those that are afforded ethics review oversight, and those that are exempt from mandatory review. The former includes "[c]ulture systems that model pre-implantation development and post-implantation development up to gastrulation by incorporating human embryonic and extraembryonic lineages, including trophoblast and extraembryonic endoderm"—for instance, blastoids and ETX-embryoids. The ISSCR recommends that research on such embryo-like structures should be reviewed by an appropriate agency which would not permit *in vitro* culture beyond the appearance of the primitive streak.

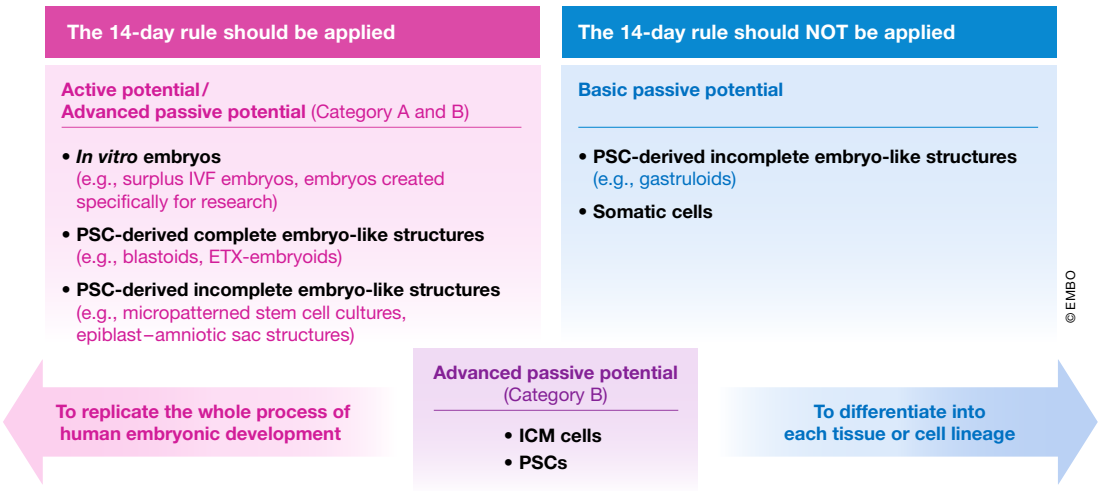


**Figure 1. Applicability of the 14-day rule.**

Other embryo-like structures would be exempted from mandatory review, since "constructs that do not attempt to model the integrated development of the entire conceptus are not equivalent to embryos" (pg 171). In the ISSCR's classification, such embryo-like structures include "[c]ulture systems that do not model the integration of all embryonic and extraembryonic lineages or models that clearly lack the potential to form a full organism"; "culture systems that model human gastrulation and subsequent stages (beyond the appearance of the primitive streak)" (for example, "models of the neural tube or micropatterned stem cell cultures forming three germ layers, or gastruloids" (pg 173)); and "[a] human embryo model that was disassembled at the time of appearance of the primitive streak into component parts for further culture or study *in vitro*" (pg 174).

Our analysis of the differing degrees of potential of embryo-like structures supports elements of Hyun *et al*'s analysis to regard PSC-derived *complete* embryo-like structures (e.g., blastoids and ETX-embryoids) as having advanced passive potential (classified in Category A). In this sense, they should have the same moral status as intact but un-implanted surplus IVF embryos and embryos created specifically for research. As we discussed, we also concur that some types of PSC-derived incomplete embryo-like structures no longer have advanced passive potential (classified in Category B). Accordingly, they should be treated similar to somatic cells or cells and tissues derived from PSCs. However, some other types of incomplete embryo-like structures—micropatterned stem cell cultures, epiblast-amniotic sac structures—still have advanced passive potential (classified in Category B). We believe that such PSC-derived incomplete embryo-like structures should be afforded the same moral protection as *in vitro* embryos and PSC-derived complete embryo-like structures with Category A advanced passive potential. This means that these types of PSC-derived incomplete embryo-like structures should not be cultured beyond the appearance of the primitive streak.

Moreover, even PSCs and ICM cells can have advanced passive potential to replicate the whole process of human embryonic development if the technology (and environment) exists for the cells to develop into humans and if there is the intention to use the technology in this way. The "technology (and environment)" may include, for example, a scaffolding matrigel that supports embryo and fetus growth and provides pressure, oxygen, carbon dioxide, nitrogen, temperature control, nutrition, and growth factors. Given this degree of advanced passive potential, we thus believe PSCs and ICM cells should also be afforded the same moral protection as embryos with Category A only when they are cultured to replicate the whole process of human embryonic development. In other words, they should fall within the scope of the current 14-day rule depending on the situation and the moral protections it affords (Fig 1).

Alternatively, one might argue that our ability to sustain embryos and embryo-like structures means that we should revise the 14-day rule and the moral protections that we afford to embryos in research. We believe that such a conclusion is too hasty. The 14-day limit was a widely accepted moral compromise after long and intense deliberation. If this rule is to change, it should do so following rigorous analysis of the ethical arguments and not as a mere response to new scientific capabilities. Whatever one thinks of the 14-day rule though, our point is one of consistency. *In vitro* embryos and PSC-derived complete embryo-like structures (Category A) should be afforded the same moral protection as Category B entities.

## Conclusion

Two new methods—*in vitro* culture methods of human embryos and embryo-like structure formation methods—could eventually mimic normal human development. This would greatly benefit research on elucidating the "black box" of human development to obtain a detailed understanding of how embryos grow and develop into fetuses. However, it also raises ethical questions about the moral status of human embryo-like structures since one of the major ethical issues in the debate on human ES cell research has been whether it is morally acceptable to destroy embryos with the potential to develop into human beings. To delineate what degree of moral status different kinds or degrees of potential to develop into a mature human being should confer, we

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***In vitro* culture of human embryos**

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divided this potential into four categories: active potential, passive potential, advanced passive potential (Category A and Category B), and basic passive potential. As many countries have based their regulation of research using human embryos on the potential to develop into a human being, we will need to include the degrees of potential of human embryo-like structures for moral consideration.

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