STEM CELL-DERIVED EMBRYO MODELS : MORAL ADVANCE OR MORAL OBFUSCATION?

ABSTRACT

Stem Cell-derived Embryo Models (SCEM) are model embryos used in scientific research to gain a better understanding of early embryonic development. The way humans develop from a single-cell zygote to a complex multicellular organism remains poorly understood. However, research looking at embryo development is difficult because of restrictions on the use of human embryos in research. Stem Cell Embryo Models could reduce the need for human embryos, allowing us to both understand early development and improve assisted reproductive technologies. There have been several rapid advances in creating SCEM in recent years. These advances potentially provide a new avenue to study early human development. The benefits of SCEM are predicated on the claim that they are different from embryos and should therefore be exempt from existing regulations that apply to embryos (such as the 14-day rule). SCEM are proposed as offering a model that can capture the inner workings of the embryo but lack its moral sensitivities. However, the ethical basis for making this distinction has not been clearly explained. In this current controversy, we focus on the ethical justification for treating SCEM differently to embryos, based on considerations of moral status.

1. NEW DEVELOPMENTS IN EMBRYO MODELLING

Stem Cell-derived Embryo Models (SCEM)[1] are used in scientific research to gain a better understanding of early embryonic development. Several pieces of recent research have produced sophisticated SCEM, which very closely mirror the internal structure and organisation of embryos.

In 2021, a research team at Monash University in Australia successfully reprogrammed induced pluripotent cells to form structures like early human embryos. These structures closely resembled normal human embryos except for lack the normal membrane that surrounds the blastocyst, meaning they cannot implant in the uterus. [1]

Also in 2022, a team from the University of Cambridge published their results of an embryo model which they claim competently develops through the stage of gastrulation, and into neurulation and organogenesis.[2] The UK model displays clear features of a developing mouse brain and heart, as well as other features of a typical 8.5-day-old mouse embryo. The authors suggest that the self-organising ability of the stem cells used to generate these embryo models make them a robust tool for understanding mammalian embryonic development.

In 2022, an Israeli lab grew mouse embryos from induced pluripotent stem cells.[3] The embryo developed inside a bioreactor, or external uterus, for eight days (approximately half a mouse's gestation period). Some cells of the embryo were stimulated with hormones which signal the development of placenta or yolk sac tissue. Other cells developed into organs and other tissues without intervention. While most of the stem cells failed, 0.5% were very similar to a natural eight-day-old embryo with a beating heart, basic nervous system, and a yolk-sac.

In 2023, the same Israeli lab was able to create model human embryos using only human pluripotent stem cells, without any genetic modifications [4]. After aggregating three lineages derived from human embryonic stem (ES) cells - these aggregates were grown in culture for 8 days. A small proportion of the resulting models recapitulated key structural and developmental hallmarks seen in human embryos between 7-14 days after fertilisation, including correct spatial organisation and emergence of embryonic disk, amniotic cavity, yolk sac, chorionic cavity and surrounding trophoblasts layers. The models appeared to undergo dynamically changing milestones resembling post-implantation human embryos, such as primordial germ cell specification and trophoblast maturation.

These recent advances in SCEMs, promise the ability to be able to study key parts of early development without the use of human embryos.

2. MOTIVATIONS FOR DEVELOPING SCEM

The way humans develop from a single-cell zygote to a complex multicellular organism remains poorly understood. Research looking at embryo development in the first seven days after conception is difficult because of restrictions on the creation of human embryos.[5] While donated excess IVF embryos are often used in research, it is considered bets practice to freeze embryos after five or six days of development [6]. As such it is difficult to use donate dIVF embryos to study the very first stages of development. While in some justifications, such as the UK, it is possible to create embryos

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[1] Some use the term 'embryoid' to describe embryo models created with stem cells.[1] However, embryoid is a contested term, because it is often used to refer to 'embryoid bodies', a less sophisticated ag
gregate structure formed with stem cells. Instead we use the term Stem Cell-derived Embryo Models (SCEM).

for the purpose of research, it is often governed by strict regulations, which makes research either unfeasible or very arduous.

Without being able to study development in the very first days after conception, much current research is based on work in mice models. [7] SCEM that mimic embryo development from the zygote stage could increase our knowledge of the first stages of human development and perhaps lead to improved assisted reproductive technologies. [8]

While excess IVF embryos can be used to study the period between 5 and 14 days after conception, many major jurisdictions explicitly prohibit the growth of embryos in the lab past 14 days [5]. While it is possible to use donated aborted foetal tissue to study embryo development after 28 days, the period of development that occurs between 14 and 28 days is essentially impossible to study. This period is often referred to as the 'black box' of human development. [9] The black box period encompasses the process of gastrulation, where embryonic cells organise into a tiny three-layered body with a primitive nervous system, muscles and gut. Gastrulation is considered a particularly important period of development. A phrase attributed to the eminent biologist Lewis Wolpert states "It is not birth, marriage or death, but gastrulation which is truly the most important time in your life."[10].

In sum, because of the research potential of SCEM there are clear scientific reasons to welcome their development. They could help improve our knowledge of currently opaque areas of human development and contribute to our understanding of human infertility.

3. JUSTIFYING SCEM OVER EMBRYOS

Several ethical concerns have been raised about the development of SCEM. Many of these reflect similar issues raised around novel reproductive technologies , including: 'unnaturalness' arguments; the commodification of human reproduction; the promotion of eugenic ideation; and safety. We wish to instead focus on the ethical justification for treating SCEM differently to embryos. The benefits of SCEM are predicated on the claim that they are different from embryos and should therefore be exempt from embryo regulations (such as the 14-day rule). SCEM are proposed as offering a model that can capture the inner workings of the embryo but lack its moral sensitivities. The ethical basis for making this distinction has not been clearly explicated.

One way of ethically justifying differential treatment between SCEM and embryos is to argue that SCEM have a lower 'moral status' than embryos. An entity's moral status is a measure of its inherit value and claim for ethical consideration.[11] Human adults with intact cognitive function can be seen as the epitome of beings with the highest possible level of moral status, or 'full' moral status. When we assert that adults possess (full) moral status, we acknowledge that their interests carry moral weight. In contrast, a rock represents a typical example of an entity without any moral status.

While it is uncontroversial that adults have (full) moral status, and rocks lack any moral status, the moral status of many entities remains controversial [12]. This includes other animals, very young and very old humans, humans in persistent vegetative states, embryos, brain organoids (three-dimensional neural tissue grown from stem cells), and now SCEM. Moral status in these entities is controversial because of a lack of agreement on which properties ground moral status. For example, one common view in philosophy is that the capacity for sentience (experiencing pleasure and pain) confers moral status to entities [13]. This has the implication is that in some cases, other animals, especially animals with advanced cognitive skills, will have a higher moral status than humans in certain states. Others believe there is something special about humans which gives human life a higher moral status regardless of our capacities. On this view, humans will always have a higher moral status than other animals, regardless of their health state.

Neither of these views attribute different moral status to embryos and SCEM. While SCEM are not created through human reproduction, they are certainly still human cells. Likewise, neither SCEM nor embryos have the capacity to feel pain or pleasure.

3.1 The potentiality argument

One property that is thought to be relevant to moral status, and which may justify making an ethical distinction between SCEM and embryos, is the potential of an entity to develop into a human being [14]. This 'potentiality' argument has been wielded by those who think that embryos have full moral status from the point of conception, and those who think potentiality only sufficient to grant embryos a (initially) low degree of moral status.[14]

For many of the SCEMs brought into existence, the scientific teams that created them have specifically stated that such models lack the capacity to result in a live birth, reflecting an intuitive view that this makes the research less ethically troubling. For example, Polo and colleagues suggest that, because of evidence from mouse models, their blastocyst-like structures generated from human pluripotent stem cells are unable to develop into viable embryos.[15] If SCEM lack the potential to result in a live birth, and the potentiality argument is correct, then this could be a way to justify treating embryos and SCEM differently.

However, the capacity to result in a live birth is something that SCEM could potentially possess. There are no biological reasons that precludes SCEM from being used to induce a pregnancy and lead to a live birth. In 2023, model primate embryos successfully induced pregnancy after being implanted in a uterus.[16] While these pregnancies were quickly miscarried, it suggests that as SCEM become increasingly sophisticated, they are likely to approach functional equivalence with embryos.

If the capacity or potential of embryos to result in live birth is morally important, it suggests scientists should focus on creating SCEM which clearly lack this capacity. Note though, this creates a tension regarding the scientific motivation for pursuing SCEM. As we discussed above, the research case for creating SCEM is to generate knowledge about human development and infertility. Restricting the creation of SCEM to models which clearly lack some features needed for successful development will reduce their usefulness in research. Additionally, it can be difficult to know if SCEM have the capacity to result in live birth without implanting them in a uterus.

The normative claims made by the potential argument have also been criticized in the literature. [17] One issue relates to logical reasoning. Just as acorns are distinct from oak trees and eggs are not the same as chickens or omelettes, we shouldn't confuse potentiality with actuality. The mere possibility or probability of a transformation doesn't mean we should treat something as if it has already been transformed. Similarly, while it's true that we all have the potential to die, given that immortality is unattainable, it doesn't mean we should be treated as if we are already deceased. [17]

Furthermore, since the advent of somatic cell nuclear transfer, it has been clear that any of the trillions of cells in our bodies could acquire the capacity to result in a new birth. If all somatic cells have the potential to result in a live birth, it suggests that all somatic cells have some degree of moral status. But this seems clearly absurd [18]. Our bodies shed millions of cells each day, a fact widely regarded as morally insignificant.

One response to this argument is to draw on a distinction between 'active' versus 'passive' potential. Aristotle distinguished between an object's passive potentiality (capacity for external changes) and an active potentiality (capacity for internal development toward perfection of its nature). Some scholars have argued that when this way of thinking is applied to embryos, it allows us to draw a distinction between embryos whose innate factors confer a capacity for developmental progression to birth, and somatic cells, that could only obtain this capacity if manipulated [19]. The distinction between active and passive potential can then save the view that embryos have a moral status based on their potentiality, whereas somatic cells, and SCEM, do not.

However, the idea that some embryos have an 'innate' potential to result in a live-birth, which somatic cells lack is difficult to make sense of. All biological entities interact with their environment, and their future development depends on those interactions. Unless an implanted embryo is supplied with nutrients and energy, via the mother, it will fail to develop into live birth. Even more clearly, embryos that are left over from IVF, require a very specific set of actions and steps to be taken to have any chance of forming a viable pregnancy. In this sense both embryos, somatic cells and SCEM require input from the environment in order to make the necessary internal changes and to guide development. Some have argued that a proper application of the Aristotelian distinction between active and passive potential would categorize both embryos and somatic cells as having an 'active' potential to result in a live birth, as all the necessary instruction required for development are contained internally (within their cell walls). [18] This reasoning can be extended to argue that SCEM also have an active potential.

Rather than drawing on the metaphysically challenging notion of 'potential', we might be able to make an ethically relevant distinction between implanted embryos, somatic cells, and SCEM based on the likelihood a future person will exist who is a descendant of the entity in question. The probability of any one of our trillions of somatic cells becoming a future person is very very tiny. Likewise, the probably of a lab created SCEM being implanted into women and developing into a human is incredibly small (given both technical and legal restraints). In contrast, an implanted embryo, located in a uterus, has a relatively good chance of resulting in a live birth and future person. If the potential to become a future person is morally significant in some way, then the empirical fact that in some cases this potential has a good chance of being realised, and in other cases next to no chance of being realised, seems morally relevant.

Note though, just as somatic cells and SCEM have a tiny probability of developing into a future person, so to do some embryos. Embryos that have been left over from IVF and donated to research, for example, individually only have a tiny probability of developing into a future person. While considerations of the probability of a future person being created might explain why SCEM have a lower moral status than implanted embryos, it may not explain why they have greater moral status than embryos donated to research.

In sum, it is difficult to point to any intrinsic or biological difference between SCEM and embryos, that justifies assigning embryos a higher moral status than SCEM.

4. SCEM AND THE 14-DAY RULE

The most pressing question regarding SCEM is whether they should be exempt from the so called "14-day rule" which limits in-vitro embryo development beyond this point.

The 14-day rule was first proposed by The Ethics Advisory Board of the US Department of Health, Education, and Welfare in 1979, and then endorsed in the UK by the influential Warnock Report [20].

It has since formed the backbone of many counties' embryo research legislation, and received the backing of many scientific groups, including the International Society of Stem Cell Research.[2]

Some jurisdictions have ruled that certain SCEM should be subject to the 14-day rule, as they fall under the legal definition of 'embryo' in current regulations. In other countries, such as the UK,[21] and Japan [22], SCEM are not treated as embryos, and therefore could be exempt from the 14-day rule.

Questions over the applicability of the 14-rule to SCEM are complicated by the dubious ethical foundation of the rule itself. When the 14-day rule was first introduced it was not technically possible to develop embryos past 14 days. The 14-day limit was not chosen because of rigorous ethical analysis, but rather "it provided a pragmatic means to allay public anxiety while delineating a clear-cut and enforceable boundary".[23]

Some ethical justifications for the 14-day limit have been offered in the literature. For example, some have argued that the fundamental purpose of the 14-day rule is to prevent the possibility of embryos experiencing pain or sentience as part of research.[24] However, it is believed that this capacity does not develop until closer to 20 weeks.[25] This consideration supports a much longer limit than 14 days. Other theorists have argued that the justification for the 14-day rule is that the formation of the primitive streak signifies the beginning of a unique human being, as it is at this stage that twinning is no longer possible.[26] One version of this argument holds that as numerical identity is not fixed before 14-days, the entity in question cannot be said to have an (active) potential to develop into a future person. However, arguments about numerical identity being morally important do not hold up to philosophical scrutiny. Dereck Parfit describes several thought experiments which show that the capacity of entities to split and have several descendants should make no difference to their current moral status. For example, imagine a future where a teleportation device makes it possible to make copies of people. Should the fact that it is possible to make copies of people ethically change how we treat them? This seems highly counter-intuitive, even if we accept the role of potentiality in moral status. For example, suppose one reason why we treat young babies as if they have full moral status is because of their potential to develop sophisticated cognitive capacities. Further, suppose we acquire the technological capacity to make copies of children, so one child is capable of having several adults as their descendants. It seems obvious that such a technological development should not lower the moral status of children in such a world.

Furthermore, the idea that embryos acquire a moral status at 14-days seem highly inconsistent with other practices. Millions abortions are performed each year, all on embryos over 14-days old, and many in jurisdictions which endorse the 14-day rule. Furthermore, millions of embryos older than 14-days are lost through natural miscarriages each year. If embryos acquired moral status at 14 days, this fact should be seen as a pressing global problem [27].

For this reason – among others – many experts are now calling for the 14-day rule to be overturned [28]. An expert body in the Netherlands recommended regulatory changes to allow embryo development to 28 days [29]. In the UK, changes to a case-by-case assessments are being considered [30]. The potential for SCEM to develop biological features faster than embryos, such that a 7-day SCEM may possess features of a 10-day embryo, suggest an approach where research is halted due

[2] The International Society of Stem Cell Research endorsed the 14-day rule in its 2016 guidelines, but not in its 2021 guidelines , which instead advocate for public debates about limits on embryo development in research

to the development of morally troubling features, is more appropriate than drawing a hard limits based on 'days'.

In the absence of the 14-day rule, are there any advantages to using SCEM to study development over embryos? SCEM might be useful because of their potential to generate huge number of genetically identical model embryos. SCEM could be used to compliment research on embryos and may be preferable for some research aims. Donated IVF embryos are heterogenous which may introduce unnecessary variability into experiments. For this reason, SCEM may play a role in research even in the absence of the 14-day rule.

However, these advantages of SCEM would disappear if we could create, clone, and genetically manipulate embryos for research. SCEM offer practical advantages for researchers in a flawed regulatory systems, rather than providing a moral advance over the use of embryos.

5. CONCLUSION

In this paper, we have argued that it is difficult to see a consistent way in which appeals to moral status can help justify the position that there is a morally relevant difference between SCEM and embryos. While SCEM provide certain practical advantageous over using embryos, especially in current regulatory systems, they offer no moral advantages over using embryos in research. The extent to which SCEM are useful in research, mirrors the extent to which they possess features which are thought to make the use of embryos morally problematic.

We have a choice: we can use both embryos and embryoids for research – and in many ways embryos are superior as they are the very entity we are wishing to study – or we can forgo both because of concerns about possible moral status. The latter position would be inconsistent with the hundreds of thousands of fetuses and embryos destroyed around the world as part of family planning. The manoeuvre to endorse SCEM as having moral advantages over embryos is an obfuscation. For countries with liberal abortion and embryo destruction laws, we should face up to the fact that there are no ethical barriers to the creation and destruction of embryos for research.

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