Article

Conscious Bias: Regulating iBlastoids

Henry Frazer

Abstract

Research into the early stages of human development has remained difficult due to ethical concerns around the use of human embryonic material. The creation of iBlastoids, which are simulations of human blastocysts created from human skin cells, offers a path that provides clearer avenues for research with the potential to sidestep ethical dilemmas. However, scientific and regulatory communities are yet to decide how to regulate these structures, and a new framework around which to judge moral worth is required. One possible avenue is to consider an organism's consciousness.

Keywords:

iBlastoids, ethics, medical ethics, stem cells, embryo research.

The ethical nature of iBlastoids has been under scrutiny ever since its discovery by Jose Polo and his team of researchers in March, 2021. An iBlastoid is a 3D cell culture which resembles the blastocyst stage of early human development, created by taking a human somatic cell and exposing it to various growth and genetic drivers to reprogram it into a model of the human embryo. This discovery was met with great excitement as the somatic origin of iBlastoids offered a potential resource for further investigation into embryonic development without requiring the use and destruction of sensitive reproductive materials. However, following the appearance of these iBlastoids, researchers notified the Australian National Health and Medical Research Council Embryo Licensing Committee (NHMRC-ERLC), which subsequently advised the team to stop generating iBlastoids pending consideration of regulation on this advancing area of research (Liu et al., 2021).

The key innovation made by Polo's team towards creating iBlastoids began with a differentiated somatic cell and rewinding its development pathway to create a cell with many developmental outcomes. iBlastoids are thus grown from a type of cell known as human-induced pluripotent stem cells (hiPSCs). The rewinding process was achieved by exposing human dermal fibroblasts to specific growth mediums as well as manipulating regulatory genes such as OCT4 and MYC. After 21 days, hiPSCs developed and were placed in AggreWell systems. AggreWells allow 3D interactions to occur within a cell culture by providing a spherical structural lattice and centrifuging cells to distribute themselves evenly throughout the system. Some of these hiPSC cultures formed blastocyst-like structures, which notably presented cavitation and 3D structures comparable to "measurements of human blastocysts at embryonic days 5-7" (Liu et al., 2021, pp. 628). These iBlastoid models offer exciting opportunities for researchers and, as the report states, will "facilitate the study of early human development" (Liu et al., 2021, pp. 627). They will be especially useful for research into the 'black box' of human development, referring to embryos during the first weeks after implantation when use of such reproductive material is restricted (Munsie & Abud, 2021). iBlastoids increase access to this material as they do not require the destruction of human embryos and are potentially less ethically contentious. Research outcomes could include understanding the effects of gene mutations, causes of infertility early in a pregnancy, and the effects of new drugs on foetal development.

While exciting, iBlastoids are not without controversy, especially around their appropriate moral status. They fall into a regulatory grey area, with various ways to interpret their nature. On one hand, viewing iBlastoids through an understanding of cell differentiation suggests that they are not morally equivalent to a standard embryo and thus offer wider research opportunities. Cell differentiation describes how all cells can contain identical genomes yet develop specialised roles. Polo's team exploited the patterns and mechanisms of cell differentiation by simulating various stages in a cell's development, even reprogramming the gene expression of skin cells to trigger regression to an earlier stage. iBlastoids generated from skin cells distinguish them from, for example, IVF embryos generated via fertilisation of an egg with a sperm. However, the concept of moral value can also be applied in the analysis of the ethical ramifications of iBlastoids. Qualifying an organism's moral value helps guide decisions around how the organism is used and destroyed.

While sometimes intuitive or societally ingrained, moral value can be ambiguous and debated. Current Australian federal law legislates against the growth of embryos in vivo beyond 14 days of development, or beyond the formation of a primitive streak (NHMRC, n.d.), which is the beginning of an embryo's nervous system. The moral value of the embryo changes when the primitive streak has developed. This is what Brown (2018) describes as the 'two substance changes' theory, because there are two developmental milestones impacting the moral status of the developing organism. However, other interpretations of moral value ignore morphological changes. These 'continuity' theories (Brown, 2018) focus more on the potential of an organism to develop and do not distinguish between various stages in that organism's growth, ascribing the same moral value to all stages.

As seen through the response of the ERLC to the team's iBlastoid discovery, the moral status of an iBlastoid is disputed. iBlastoids resemble a human blastocyst and while the extent of their developmental potential remains unclear, they could have the potential to form life. At this stage, the Australian regulator has decided that Australia's laws governing embryo research also apply to iBlastoids (NHMRC, 2023). However, Polo, among others, disputes this conclusion. Polo had stated that he did not feel like he had created life (Mannix, 2021) and points to many differences between an iBlastoid and an embryo, including the lack of the crucial zona pellucida (Liu et al., 2021), which is the extra-cellular matrix surrounding human oocytes that is essential for fertilisation and growth. Indeed, the implications of cell differentiation suggest that the genesis of an iBlastoid from somatic skin cells must fundamentally differentiate them from other embryos and precursors. iBlastoids are derived from somatic skin cells, not gametes, and if they are given similar or equal status to standard embryos, that could extend that status to all skin cells, which have the potential to become an iBlastoid – a seemingly absurd outcome.

This dispute over regulation is part of a wider push from some parts of the scientific community to rethink the way we regulate iBlastoids, embryos and other organisms related to human development altogether. In an article published in Science, Insoo Hyun and colleagues advocated for a "cautious, stepwise approach to scientific exploration beyond the 14-day limit" (Hyun et al., 2021, pp. 998). They discussed that when the 14-day norm was established, the technology to go beyond that did not exist. They suggested that this limit as somewhat arbitrary, and cite the significant scientific yields that we could benefit from if work beyond the limit was allowed. But for the 14-day limit to be discarded, some justification for a new limit must be found. One possible route could be the consideration of an organism's consciousness. Not only does consciousness traditionally mark a significant step up in the moral value of an organism, it also requires a certain level of cell specialisation to occur as pre-neuronal cells turn into neurons (Reardon, 2020). Indeed, the creation of iBlastoids has shown the research community that through cell differentiation, a wide range of growth outcomes is possible. Thus, the cellular origins of a lab-grown organism become less important, whilst the outcomes of the cells themselves actually define our ethical and moral responsibilities. In assigning moral value to organisms, Savulecsu argues "what does matter is our mind... once an organism has this, we are in ethically controversial territory" (2021, para. 12). This would appear to be a logical and promising point to begin future discussions around regulation of iBlastoids and other developmental technologies, both enabling more research and preventing the

creation of conscious lab-grown organisms.

Due to their arguably less complicated moral status when compared to standard embryos, and thus their exciting opportunities for research, iBlastoids appear to offer society more prospects than perils. Yet current regulation is proving a roadblock for this potential. No major research articles have been published since the initial excitement in March 2021, as the guidelines enforced by the ERLC have left little room for further investigation. To unlock the potential of iBlastoids, the arbitrary 14-day limit guiding all research into early human development should be discarded in favour of an evidence-based, philosophically informed regulatory framework. Consciousness, while still not fully understood by the scientific community, could prove a valuable focus for this new system of ethical oversight. A recentering around consciousness could provide a balance between a respectful and sensitive approach towards the manipulation of human reproductive material while also allowing valuable further research to be carried out.

References

Brown, M, T. (2018). The Moral Status of the Human Embryo, *The Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine*, *43* (2), 132–158. https://doi.org/10.1093/jmp/jhx035

Hyun, I., Bredenoord, A., Briscoe, J., Klipstein, S., & Tan, T. (2021). Human embryo research beyond the primitive streak. *Science*, *371*(6533), 998-1000.

Liu, X., Tan, J. P., Schröder, J., Aberkane, A., Ouyang, J. F., Mohenska, M., Lim, S. M., Sun, Y. B. Y., Chen, J., Sun, G., Zhou, Y., Poppe, D., Lister, R., Clark, A. T., Rackham, O. J. L., Zenker, J., & Polo, J. M. (2021). Modelling human blastocysts by reprogramming fibroblasts into iBlastoids. *Nature*, *591*(7851), 627-632. https://doi.org/10.1038/s41586-021-03372-y

Mannix, L. (2021, March 18). Scientists create model embryos, raising ethical questions. *The Sydney Morning Herald.* https://www.smh.com.au/national/scientists-create-model-embryos-in-lab-raising-major-ethical-questions-20210317-p57bkc.html

Munsie, M., & Abud, H. (2021, March 18). Researchers have grown 'human embryos' from skin cells. What does that mean, and is it ethical? *The Conversation.* https://theconversation.com/researchers-have-grown-human-embryos-from-skin-cells-what-does-that-mean-and-is-it-ethical-157228

National Health and Medical Research Council. (n.d.). *Embryo Research Licensing, Commonwealth and State Legislation*. Australian Government. https://www.nhmrc.gov.au/research-policy/embryo-research-licensing/commonwealth-and-state-legislation

National Health and Medical Research Council. (2023). *NHMRC statement on iBlastoids*. Australian Government.https://www.nhmrc.gov.au/about-us/news-centre/nhmrc-statement-iblastoids

Reardon, S. (2020). Can lab-grown brains become conscious? *Nature*, 586, 658-661. https://doi.org/10.1038/d41586-020-02986-y

Savulescu, J. (2021, March 18). Ethics, iBlastoids, and brain organoids: Time to revise antiquated laws and processes. *The Journal of Medical Ethics Forum*. https://blogs.bmj.com/medical-ethics/2021/03/18/ethics-iblastoids-and-brain-organoids-time-to-revise-antiquated-laws-and-processes/