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AUTHOR(S):

Sawai, Tsutomu; Akatsuka, Kyoko; Okui, Go;
Minakawa, Tomohiro

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The regulation of human blastoid research

A bioethical discussion of the limits of regulation

Tsutomu Sawai^{1,2,*} , Kyoko Akatsuka³ , Go Okui²  & Tomohiro Minakawa⁴ 

Developmental research has made considerable progress modeling either part of or the entire embryonic development of both humans and non-human animals. A major step forward was the ability to grow blastocyst-like structures from pluripotent stem cells: these structures, known as “blastoids,” mimic early embryonic development up to and potentially beyond the blastocyst stage 5–6 days after the first cell division. Blastoids have attracted considerable attention as an effective research tool to understand early human development and to elucidate the causes of infertility, teratogenesis, and other developmental abnormalities.

“... many scientists see the use of human blastoids as an exciting scientific opportunity, as it may help to reduce the need for human embryos in research.”

Until now, research with blastoids has mainly studied early development in mice, but, as of 2021, research results are also being reported from human blastoids (see “Further Reading”). Indeed, many scientists see the use of human blastoids as an exciting scientific opportunity, as it may help to reduce the need for human embryos in research (Ravindran, 2021). However, as with any research that uses human embryos or human stem cells derived from embryos, human blastoid research raises ethical questions and is subject to regulation and

approval. The latest ISSCR guidelines state that “[f]orms of research with embryos ... and stem cell-based embryo models ... are permissible only after review and approval through a specialized scientific and ethics review process” (ISSCR, 2021). Thus, although blastoids are models of embryonic development, they are currently considered to require the same or similar ethical considerations as blastocysts or cells derived from human embryos. In fact, Australia made a decision to regulate blastoid research in the same manner as research on human embryos (Australia NHMRC, 2021).

A question of equivalence

Some scientists have argued that blastoids and blastocysts are not functionally equivalent (Rivron *et al*, 2018), and would therefore not require the same level of oversight and regulation as human embryos. Others, however, have been arguing that blastoids will become functionally closer to blastocysts sooner or later if they are morphologically and genetically similar to normal blastocysts in many respects (Zheng & Fu, 2021). Consequently, blastoids and blastocysts should be treated the same in terms of regulation as they may become functionally equivalent in the future.

The normative claims of these opposing camps hold a common premise in that the regulation of blastoids should be determined according to their functional equivalence to blastocysts in terms of their developmental capacity. The difference here is the two sides’ attitudes toward regulation, namely whether one places greater focus on empirical demonstrability or theoretical possibility

with regard to the question of functional equivalence.

As one might glean from the cautious wording of the ISSCR guidelines, even scientists who argue that blastoids and blastocysts are functionally different at present, are not denying the possibility that they might end up being close to functionally equivalent at some point in the future. Looking further back, the same issues arose regarding cloning techniques that were developed in the late 1990s: the cloned sheep Dolly is a plausible reason to treat cloned embryos as equivalent to “normal” embryos.

“... although blastoids are models of embryonic development, they are currently considered to require the same or similar ethical considerations as blastocysts or cells derived from human embryos.”

Moreover, theoretical possibilities can sometimes be inferred from empirical evidence. To be able to conduct a constructive discussion regarding the ethics and legal regulations of blastoid research, it is crucial to understand the extent to which blastocysts and blastoids are functionally equivalent according to present scientific knowledge and to determine whether blastoids are likely to become functionally equivalent to blastocysts in the future. Suppose that blastoids are demonstrated to possess the potential to develop into

1 Graduate School of Humanities and Social Sciences, Hiroshima University, Hiroshima, Japan
2 Institute for the Advanced Study of Human Biology (ASHBi), Kyoto University, Kyoto, Japan
3 Uehiro Research Division for iPS Cell Ethics, Center for iPS Cell Research and Application, Kyoto University, Kyoto, Japan
4 Department of Cellular and Tissue Communication, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
*Corresponding author. E-mail: tstmsw@hiroshima-u.ac.jp

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entities that resemble actual embryos. In this eventuality, the question may arise as to how one ought to distinguish the moral and legal status of blastoids and blastocysts, and therefore how to distinguish and regulate blastoid research as distinct from blastocyst research. Of course, the reliability of claims of the functional equivalence of blastoids to blastocysts in terms of their developmental capacity may also be an ethical issue in itself (Piotrowska, 2020).

“... it is crucial to understand the extent to which blastocysts and blastoids are functionally equivalent according to present scientific knowledge...”

The aim of this article is not to determine the moral, ontological, or legal status of blastoids, nor to adopt a specific attitude on the ethics of blastoid research—there have already been several reports on the ethics of blastoid research (see “Further Reading”). Rather, we will examine a set of ethical positions that would inform the regulation of blastoid research, and suggest directions in policy and societal debates.

Blastocysts and blastoids: in what ways are they the same and in what ways different?

Generally speaking, blastoids are structurally, genetically, and functionally similar in certain aspects to blastocysts in mice and humans. At the structural and genetic level, both are similar in terms of the morphology and number of cells, and both contain the same major cell lineages as has been shown by transcriptome analysis. At the functional level, they are also similar insofar as both blastoids and blastocysts are capable of implantation into a uterus. However, while blastocysts continue their normal development to the gastrula stage and eventually into a fetus, blastoid development is soon halted. The cause might be the absence of a zona pellucida, which mainly prevents polyspermy and ectopic pregnancy, but it is still unknown to what extent the zona pellucida affects postimplantation development. It should also be noted that the extent to which blastoids generally reproduce the

development of normal blastocysts is as yet unknown.

Indeed, as has been inferred from mouse experiments, blastoids do not possess the ability to develop into the fetal stage, because the implantation of blastoids does not lead to development, and human blastoids are thought to be similarly incapable of development. However, it is important to note that the experimental methods to test the developmental ability of blastoids are by necessity different in mice and humans. Moreover, it would not be socially and legally permissible to implant a blastoid into the uterus of a woman. Thus, the ability of human blastoids to continue normal embryonic development must be inferred on the basis of how non-human blastoids develop.

“... the ability of human blastoids to continue normal embryonic development must be inferred on the basis of how non-human blastoids develop.”

In addition, developmental abnormalities are likely caused by culture techniques for blastoids and blastocysts that do not fully mimic *in utero* development. Theoretically, blastoids, whether mouse or human, could therefore undergo *in vitro* development if culture techniques became available that perfectly mimic *in utero* development; as a result, blastoids would more closely resemble blastocysts in terms of developmental potential. Although the *in vitro* culture of embryos has itself been subject to notable improvement and despite promising results (Shahbazi et al, 2016), the extent to which the *in vitro* culture of blastoids is feasible is not yet clear. Generally, *in vitro* culture techniques that would allow extrauterine development still remain speculative.

There have been no reports yet of mice blastoids developing to the fetal stage: this may be the result of specific differences between blastocysts and blastoids or current *in vitro* culture techniques. As it is unclear when these differences will be overcome, any speculations that blastoids are equivalent to blastocysts or that blastoids will become equivalent to blastocysts in the near future are not supported by current scientific evidence.

Ethics and regulatory options for blastoid research

Taking into account these arguments, there are two options for regulating blastoid research. One is to differentiate between blastoids and blastocysts since there is at present no convincing evidence to demonstrate that blastoids and blastocysts are functionally equivalent or are likely to become functionally equivalent in the near future. The other possibility is to regulate them in the same way, assuming that they may become functionally equivalent at some point in the future. Hence, if the evidence of functional equivalence is the basis for regulation, since currently there is no such evidence, the first possibility, a pro-actionary approach to err on the side of regulating too loosely appears to be the more plausible option, whereas a precautionary approach to err on the side of regulating too strictly may seem less convincing.

Different national legislative systems have already responded to this uncertainty. Japan has adopted the view—albeit unofficially—that there is no scientific consensus yet whether blastoids are capable of ontogenesis if they are implanted into the uterus. Its regulation therefore treats blastoids differently from blastocysts (Yui et al, 2022). Both the USA and the UK have adopted the same position (Matthews & Morali, 2020). Australia, by contrast, has taken the position that blastoids should be treated in the same way as embryos given certain morphological similarities between blastoids and embryos, and given that some of those similarities are consistent with the regulatory definition of “embryo” (Australia NHMRC, 2021). The Australian Research Involving Human Embryos Act of 2002 defines an embryo as “a discrete entity that has arisen from either: (a) the first mitotic division when fertilisation of a human oocyte by a human sperm is complete; or (b) any other process that initiates organised development of a biological entity with a human nuclear genome or altered human nuclear genome that has the potential to develop up to, or beyond, the stage at which the primitive streak appears; and has not yet reached 8 weeks of development since the first mitotic division.” The iBlastoid created by Jose Polo and colleagues at Monash University therefore meets definition (b) of an embryo.

However, morphological similarity does not necessarily mean that blastoids and

blastocysts should be treated similarly. Moreover, treating blastoids under the same regulatory framework as blastocysts do not automatically entail a ban on blastoid creation. The two regulatory options have both advantages and disadvantages (Table 1).

“... treating blastoids under the same regulatory framework as blastocysts do not automatically entail a ban on blastoid creation.”

The main advantage of treating blastoids and blastocysts differently is that it gives scientists options for avoiding using blastocysts in research, which has various ethical problems. However, this position does not necessarily mean that the ethical issues have been avoided as biological differences between blastoids and blastocysts does not necessarily entail a common understanding of the moral differences between the two. Thus, even if we adopt the first position, some might still consider the creation and use of blastoids for research purposes to be ethically problematic.

Even if the functions of blastoids and blastocysts are not equivalent, the major advantage of treating them in the same way is that it avoids any potential moral wrongdoing that might result from treating them differently. However, this position has an inherent weakness: if the cause of a blastoid’s failure to develop normally depends on factors other than *in vitro* culture technology, it can be perceived as an unnecessary impediment to the progress of research. In addition, if one treats blastoids in the same way as blastocysts *without* questioning whether the failure of blastoid development is due to *in vitro* culture techniques, it would cause other discrepancies in existing regulations on the research on human embryos, particularly with respect to embryonic stem cell (ESC)

research and induced pluripotent stem cell (iPSC) research.

The ethical issues related to iPSC research are usually considered less severe than those for ESC research, which involves the destruction of embryos (Devolder, 2015). When blastoids are created from ESCs, they could fall under the regulatory framework of embryos that have been created for research purposes. By contrast, when blastoids are created from iPSCs, it might be more reasonable to consider them within the regulatory framework of cloned embryos created via somatic cell nuclear transfer (SCNT) for research purposes. Nonetheless, many countries regard cloning embryos for research purposes—or “therapeutic cloning”—as more ethically challenging than creating embryos by sperm and eggs for research purposes (Devolder, 2015). Thus, the creation of blastoids from iPSCs could be deemed to be more ethically problematic than the creation of blastoids from ESCs.

Resolving discrepancies

There are at least three options for how to resolve these regulatory discrepancies. The first is to treat any embryo that is created for research purposes uniformly as a “research embryo.” This approach stipulates that, irrespective of whether it is a cloned embryo or a blastoid from either ESCs or iPSCs, the degree of ethical consideration would remain the same. This eliminates concerns about whether blastoids derived from pluripotent stem cells such as iPSCs and ESCs should be treated as cloned or research embryos. However, it would also make it more challenging, at least in some cases, to use blastoids in research, even though blastoids were originally developed to avoid the use of embryos.

It would also reduce the ethical significance of embryo models, including blastoids, which many scientists have emphasized. This approach may also face objections from

those who approve of the creation and use of research embryos by sperm and eggs but not the creation and use of cloned embryos.

The second option is to consider an embryo as *not* distinct from any other biological specimen in terms of its ethical evaluation. As a result of this, any research using embryos, whether it is a cloned embryo, a research embryo or a blastoid, would fall under the regulation of research using any other human tissue.

The third option is to prioritize the creation of blastoids from ESCs rather than the creation of cloned embryos, which poses more ethical problems. However, this might even increase the demand for ESCs to produce blastoids and ultimately risk that blastoid research becomes entangled in ESC research—which is considered more ethically problematic than iPSC research. However, this complicity would not pose a significant issue to begin with if ESC research itself were not considered ethically problematic.

Given the national laws and regulations on embryo research (Matthews & Moralí, 2020), it would seem to be both impractical and ethically unacceptable to pursue the second option to resolve the issues. This approach is not compatible with existing embryo research regulations and the moral respect afforded to human embryos. Thus, either the first measure—that treats any embryo that is created for research purposes uniformly as a “research embryo”—or the third option that prioritizes the creation of blastoids from ESCs rather than the creation of cloned embryos would be a more consistent position. However, either option would still pose a vexing ethical challenge to scientists or national legislative systems, which take the position that embryonic and ESC research per se is ethically problematic.

Conclusion

At present, there is insufficient evidence to assert that blastoids are functionally

Table 1. Advantages and disadvantages of the two possible regulatory regimes for research on human blastoids.

Positions	Different moral and legal status given to blastoids	Same moral and legal status given to blastoids
	<ul style="list-style-type: none"> Blastoids and blastocysts are not functionally equivalent They should be treated differently 	<ul style="list-style-type: none"> Blastoids and blastocysts are morphologically similar Blastoids and blastocysts should be treated in the same way
Advantages	<ul style="list-style-type: none"> Scientists can avoid using blastocysts in research 	<ul style="list-style-type: none"> Scientists can avoid moral wrongdoing even in case blastoids, and blastocysts turn out to have the same moral status
Disadvantages	<ul style="list-style-type: none"> The ethical issues have not been avoided (criticism remains) 	<ul style="list-style-type: none"> It can be perceived as an unnecessary impediment to the progress of research
Countries	<ul style="list-style-type: none"> UK, US, Japan (ad referendum) 	<ul style="list-style-type: none"> Australia

equivalent to blastocysts. However, it would be premature to conclude that blastoids should not be subject to ethical scrutiny. In light of the debate over the moral status of human embryos, we can interpret the moral status of blastoids based on intrinsic and relational properties in addition to potentiality. Regarding intrinsic properties, the question is whether a blastoid retains sentience—the ability to feel pain and pleasure—or even self-consciousness. Many have thought that more sophisticated cognitive architectures make room for more complex conscious experiences and more complex, morally significant, mental states such as interests concerning one’s self and the future. Concerning relational properties, that entity could be an object of ethical consideration if it has symbolic value in a community, or if people show a vested interest in said entity. Lastly, potentiality, as we discussed in this article, entails the potential of a blastoid to grow into a fetus with intrinsic and relational properties that would justify a higher moral status. We do not offer a full discussion here about intrinsic and relational properties, but rather point out that, given their potential to grow beyond the blastocyst stage, human blastoids will require further bioethical debate on these issues.

“If blastoids are to be regarded as embryos, it will become necessary to reconsider the issue of “research embryos created from sperm and eggs” versus “cloned embryos.”

We have discussed the advantages and disadvantages of considering blastoids as embryos or as research models by postulating as a normative assumption the claim that the regulation of blastoids should be based on functional equivalence to blastocysts in regard to their developmental capacity. If blastoids are to be regarded as embryos, it will become necessary to reconsider the issue of “research embryos created from sperm and eggs” versus “cloned embryos.” It would also create further ethical challenges in blastoid creation depending on the source cells: ESCs or iPSCs.

Human developmental research using blastoids has great scientific and medical potential to understand early embryonic

Box 1. Further Reading

Mouse blastoid research

- Rivron NC, Frias-Aldeguer J, Vrij EJ, Boisset J-C, Korving J, Vivivié J, Truckenmüller RK, van Oudenaarden A, van Blitterswijk CA, Geijsen N (2018) Blastocyst-like structures generated solely from stem cells. *Nature* 557: 106–111
- Vrij EJ, Scholte op Reimer YS, Frias Aldeguer J, Misteli Guerreiro I, Kind J, Koo B-K, van Blitterswijk CA, Rivron NC (2019) Chemically-defined induction of a primitive endoderm and epiblast-like niche supports post-implantation progression from blastoids. *bioRxiv* 1: 510396 10.1101/510396 [PREPRINT]
- Sozen B, Cox AL, De Jonghe J, Bao M, Hollfelder F, Glover DM, Zernicka-Goetz M (2019) Self-organization of mouse stem cells into an extended potential blastoid. *Dev Cell* 51: 698–712
- Li R, Zhong C, Yu Y, Liu H, Sakurai M, Yu L, Min Z, Shi L, Wei Y, Takahashi Y et al (2019) Generation of blastocyst-like structures from mouse embryonic and adult cell cultures. *Cell* 179: 687–702
- Kime C, Kiyonari H, Ohtsuka S, Kohbayashi E, Asahi M, Yamanaka S, Takahashi M, Tomoda K (2019) Induced 2C expression and implantation-competent blastocyst-like cysts from primed pluripotent stem cells. *Stem Cell Reports* 13: 485–498

Human blastoid research

- Yu L, Wei Y, Duan J, Schmitz DA, Sakurai M, Wang L, Wang K, Zhao S, Hon GC, Wu J (2021) Blastocyst-like structures generated from human pluripotent stem cells. *Nature* 591: 620–626
- Yanagida A, Spindlow D, Nichols J, Dattani A, Smith A, Guo G (2021) Naive stem cell blastocyst model captures human embryo lineage segregation. *Cell Stem Cell* 28: 1016–1022
- Kagawa H, Javali A, Khoei HH, Sommer TM, Sestini G, Novatchkova M, Scholte op Reimer Y, Castel G, Bruneau A, Maenhoudt N et al (2021) Human blastoids model blastocyst development and implantation. *Nature* 601: 600–605
- Sozen B, Jorgensen V, Weatherbee BAT, Chen S, Zhu M, Zernicka-Goetz M (2021) Reconstructing aspects of human embryogenesis with pluripotent stem cells. *Nat Commun* 12: 5550
- Liu X, Tan JP, Schröder J, Aberkane A, Ouyang JF, Mohenska M, Lim SM, Sun YBY, Chen J, Sun G et al (2021) Modeling human blastocysts by reprogramming fibroblasts into iBlastoids. *Nature* 591: 627–632
- Fan Y, Min Z, Alsolami S, Ma Z, Zhang E, Chen W, Zhong K, Pei W, Kang X, Zhang P et al (2021) Generation of human blastocyst-like structures from pluripotent stem cells. *Cell Discov* 7: 81
- Min Z, Zhong K, Luo Y, Fan Y, Yu Y (2022) Protein expression landscape defines the formation potential of mouse blastoids from EPSCs. *Front Cell Dev Biol* 10: 840492

Ethics of blastoid research

- Aach J, Lunshof J, Iyer E, Church GM (2017) Addressing the ethical issues raised by synthetic human entities with embryo-like features. *Elife* 6: e20674
- Nicolas P, Etoc F, Brivanlou A (2021) The ethics of human-embryoids model: a call for consistency. *J Mol Med (Berl)* 99: 569–579
- Pera MF, de Wert G, Dondorp W, Lovell-Badge R, Mummery CL, Munsie M, Tam PP (2015) What if stem cells turn into embryos in a dish? *Nat Methods* 12: 917–919
- Pereira Daoud AM, Popovic M, Dondorp WJ, Trani Bustos M, Bredenoord AL, Chuva de Sousa Lopes SM, van den Brink SC, Roelen BAJ, de Wert GMWR, Heindryckx B (2020) Modeling human embryogenesis: embryo-like structures spark ethical and policy debate. *Hum Reprod Update* 26: 779–798
- 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 et al (2018) Debate ethics of embryo models from stem cells. *Nature* 564: 183–185
- Sawai T, Minakawa T, Pugh J, Akatsuka K, Yamashita JK, Fujita M (2020) The moral status of human embryo-like structures: potentiality matters? *EMBO Rep* 21: e50984

development and the causes of developmental disorders. Thus, a discussion of the moral and ontological status of blastoids is vital to ensure a professional ethical approach informed by the regulatory options presented in this paper and construct a proper condition for blastoid research.

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References

- Australia NHMRC (2021) NHMRC statement on iBlastoid. <https://www.nhmrc.gov.au/about-us/news-centre/nhmrc-statement-iblastoids>
- Devolder K (2015) *The ethics of embryonic stem cell research*. Oxford: Oxford University Press
- International Society for Stem Cell Research (ISSCR) (2021) Guidelines for stem cell research and clinical translation, 2021 update. https://www.isscr.org/docs/default-source/all-isscr-guidelines/2021-guidelines/isscr-guidelines-for-stem-cell-research-and-clinical-translation-2021.pdf?sfvrsn=979d58b1_4
- Matthews KRW, Moralí D (2020) National human embryo and embryoid research policies: a survey of 22 top research-intensive countries. *Regen Med* 15: 1905–1917
- Piotrowska M (2020) Avoiding the potentiality trap: thinking about the moral status of synthetic embryos. *Monash Bioeth Rev* 38: 166–180
- Ravindran S (2021) Embryo-like models shed fresh light on early human development. *Nature* 600: 767–769
- 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 et al (2018) Debate ethics of embryo models from stem cells. *Nature* 564: 183–185
- Shahbazi M, Jedrusik A, Vuoristo S, Recher G, Hupalowska A, Bolton V, Fogarty NNM, Campbell A, Devito L, Ilic D et al (2016) Self-organization of the human embryo in the absence of maternal tissues. *Nat Cell Biol* 18: 700–708
- Yui H, Muto K, Yashiro Y, Watanabe S, Kiya Y, Kamisato A, Inoue Y, Yamagata Z (2022) Comparison of the 2021 International Society for Stem Cell Research (ISSCR) guidelines for “laboratory-based human stem cell research, embryo research, and related research activities” and the corresponding Japanese regulations. *Regen Ther* 21: 46–51
- Zheng Y, Fu J (2021) First complete model of the human embryo. *Nature* 591: 531–532



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