Research Guidelines for Embryoids

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Abstract

Human embryo models formed from stem cells—known as embryoids—allow scientists to study the elusive first stages of human development without having to experiment on actual human embryos. But clear ethical guidelines for research involving embryoids are still lacking. Previously, a handful of researchers put forward new recommendations for embryoids, which they hope will be included in the next set of International Society for Stem Cell Research (ISSCR) guidelines. Although these recommendations are an improvement over the default approach, they are nonetheless unworkable, because they rely on a poorly conceived notion of an embryoid's "potential" to trigger stringent research regulations.

Section 1: Introduction

International ethical guidelines for research involving human subjects have long considered human organisms inviolable for experimental purposes. Without informed consent, it is not permissible to perform experiments or do research on competent human subjects. For research involving incompetent human subjects, the researchers must seek informed consent from legally authorized representatives, and the research must entail only minimal risk and minimal burdens (along with several additional requirements).[1] A notable exception to this general constraint is experimentation involving *in vitro* human embryos. Although some have argued (and continue to argue) that human embryos have the potential to become human beings and should therefore be afforded the same, stringent research protections as fully developed human beings, regulatory bodies of at least a dozen top research-intensive countries,[2] have

largely adopted recommendations from two reports: the 1979 US Department of Health, Education, and Welfare report[3] and the 1984 UK Warnock report.[4] Both reports recommend allowing *in vitro* experimentation on human embryos younger than 14 days, after which point the embryo must be destroyed. The justification for this recommendation relies in part on the fact that during the first two weeks of development, the human embryo is 1) not yet an individual (it can still twin) and 2) not yet capable of feeling pain (it has not developed a primitive streak (PS) which is a precondition for the development of the capacity to feel pain).[5] Of course, the committees that wrote the reports were fully aware that human development is continuous and that the "14-day rule" was somewhat arbitrary, but given the aim of establishing a clear and pragmatic boundary for legally enforceable regulation, the rule seemed appropriate and has since proven quite successful. Indeed, its chief virtue seems to be that it establishes a discrete boundary, one that marks the embryo's acquisition of its special, experimentally inviolable moral status.

However, human embryo models formed from stem cells—known as embryoids—pose problems for this long-held staple of public policy because they need not develop in the same manner as regular embryos. They can, for example, be engineered to bypass the formation of the primitive streak as well as model stages of development that normally occur after the two-week mark within two weeks. Because of their manipulability, the justificatory basis for the regulations governing embryos largely lose their grip on research involving embryoids. Consequently, we should think anew about the basis of public policy involving them.

In response to the shortcomings that emerge when we try to apply existing embryo guidelines to embryoids, Insoo Hyun et al.[6] have put forward new recommendations, which they hope will be included in the next set of guidelines produced by the International Society for Stem

Cell Research (ISSCR). Although they are an improvement over the alternative, their proposed recommendations face serious problems. My aim in this essay is to bring those problems to light and offer an alternative approach for thinking about research guidelines involving embryoids.

The paper will first review reasons for refusing to extend regulations governing embryos (i.e., 14-day rule) to embryoids. It will then summarize Hyun et al.'s alternative and explain how it avoids many of the problems raised in the first section. Next, the paper will argue that, despite its virtues, the adoption of Hyun et al.'s alternative by the ISSCR is unworkable, relying as it does on the poorly conceived notion of an embryoid's "potential" to trigger stringent research regulations. Last, it will offer concluding thoughts about best practices for regulating research involving embryoids.

Section 2: 14-Day Rule and Embryoids

Embryoids have a relatively short history. In 2014, scientists discovered that when embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) are geometrically confined and given the right combination of growth factors, they can spontaneously organize to resemble human embryos.[7] Using this method, scientists have been able to model early stages of human development, including the blastocyst (day 5) stage,[8] formation of the amniotic sac (day 8),[9] gastrulation (day 17),[10] and neurulation (day 18).[11] Although all of these embryoids are incomplete in some way, scientists are constantly working to overcome existing limitations. One example of recent progress is a microfluidic device, developed by a team led by Jianping Fu, that can reliably produce a dozen embryoids in just a few days.[12] The system has a central channel that mimics the wall of the uterus and is flanked by a channel feeding stem cells and another

providing chemical signals to guide development. According to Fu, in conventional 3D cultures, less than 5% of stem cell clusters form embryoids. That success rate rises above 90% with microfluidic devices that can precisely control the culture environment.[13] Given the rate of scientific progress in this area, and the fact that the field of stem cell embryology is still in its infancy, I think it is worth taking seriously the suggestion of Nicolas Rivron and colleagues that "a major international discussion is needed to help guide this research."[14]

The discussion about what principles should guide research involving embryoids should begin by noticing that the main principle governing regular embryos is ill-suited to the task. The 14-day rule was designed as a discrete marker, indicating a clear boundary before morally significant features of embryos begin to appear.[15] But in embryoids, the emergence of these features can be suppressed (or hastened). As John Aach and colleagues[16] explain, embryoids do not tend to follow "canonical embryogenesis," the standard sequence of stages understood to comprise normal embryonic development. Instead, they tend to develop the primitive streak and the capacity to individuate out of order or not at all. Here is one example. In an experiment conducted by Yi Zheng and colleagues, embryoids were engineered to develop later stages of development in less time, such that after 36 hours, 92% of them resembled human embryos "before the onset of gastrulation at 7-12 days post-fertilization."[17] In other words, after a day and a half, the embryoid developed features that it would take regular embryos a week (roughly) to develop. In another experiment, embryoids were able to mimic gastrulation—including the development of the three germ layers and the trophectoderm—but they bypassed the formation of the primitive streak.[18] In light of these examples, a rule that uses number of days or the appearance of the PS as relevant markers is not going to reliably track what we take to be morally salient. The rule has come untethered from the features it was meant to protect and

consequently should be replaced.

Section 3: Recommendations to the ISSCR

In response to this problem, Hyun et al. have proposed six recommendations to the ISSCR for regulating research involving embryoids (see Box 1).

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Box 1 Hyun et al.'s Recommendations to the ISSCR

1. Culture systems that model pre-implantation development and post-implantation development up to gastrulation by incorporating human embryonic and extraembryonic lineages, including the trophoblast and extraembryonic endoderm, with the intent to represent the integrated development of the entire conceptus up to the appearance of the primitive streak (for example, blastoids or ETX models) are permissible only following oversight by EMRO in the United States or equivalent ethics review elsewhere (or more extensive review where local regulations require it).
2. Culture 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 are exempt from mandatory review but are notifiable to the EMRO or equivalent and subject to review should the cognizant body deem it necessary.
3. Culture systems that model human gastrulation and subsequent stages (beyond the appearance of the primitive streak) are exempt from mandatory review if they do not encompass all major lineages of the conceptus (embryonic and extraembryonic) in an intact construct and are aimed at

studying a discrete and defined period of development or discrete set of anatomic structures, rather than modeling the continuous development of an intact embryo or fetus (for example, models of the neural tube or micropatterned stem cell cultures forming three germ layers, or gastruloids). Such research would be notifiable to the EMRO or equivalent and subject to review should the cognizant body deem it necessary.

4. 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* would no longer be subject to the strict considerations suggested in (1) and may be determined to be exempt from further committee review.

5. The *in vitro* combination of human embryo models with animal or human cells or tissues or embryos should be subject to the same limitations in (1) and (2) above and mandatory review. This category would include *in vitro* human/animal embryo model chimeras, embryo model/human embryo chimeras, or any of these constructs implanted *in vitro* into explanted uterine tissues or uterine organoids.

6. No human embryo model in any of the above categories shall be transferred *in vivo* into the uterus of an animal or human.[19]

<End of Box>

I will be focused only on the first three. According to the first recommendation, embryoids that are very similar to human embryos and aim to model continuous development should be treated like human embryos (they should go through mandatory ethical review by the Embryo Research Oversight (EMRO) committee or equivalent ethics review elsewhere, and only be allowed to develop up to the appearance of the PS), because they have the potential to develop into a human

being. According to the second recommendation, embryoids that aim to model continuous development but are not very similar to human embryos should not be treated as such (they need not go through mandatory ethical review by the EMRO or equivalent), because they lack the potential to develop into a human being. And according to the third recommendation, embryoids that do not aim to model continuous human development but instead aim to model "a discrete and defined period of development or discrete set of anatomic structures"[20] should similarly not be treated like embryos (they should be exempt from mandatory ethical review by the EMRO or equivalent) if they lack the potential to develop into a human being.

Thus, based on these recommendations, only embryoids that are very similar to regular embryos (i.e., they have all the relevant parts and are developing along the same trajectory) should undergo the stringent ethical review mandatory for human embryos and be prevented from developing past the appearance of the PS. Embryoids that do not have all the relevant parts and are therefore not developing along the same trajectory as regular human embryos, are exempt from the stringent mandatory ethical review.[21]

Because Hyun et al.'s recommendations to the ISSCR recognize the realities of biotechnological advancement, they are an improvement over the 14-day rule. In particular, it is praiseworthy that they provide guidance for research involving embryoids designed to diverge from canonical development. It is also commendable that they do not simply extend the 14-day rule to all embryoids, recognizing instead that different embryonic models need to be treated differently based on what they are modeling. But these positive features of Hyun et al.'s recommendations are not enough. Indeed, the fact that Hyun et al.'s recommendations rely on the "potential" (or absence of it) of an embryoid to develop into a human being to distinguish how they should be treated is deeply problematic for three reasons: first, the recommendations

thereby become subject to the same type of criticism that was leveled against researchers seeking alternative sources of stem cells; second, the recommendations are thereby threatened by reductio ad absurdum arguments; and third, the recommendations seem to thereby exempt problematic research proposals from stringent ethical review.

First, according to Hyun et al.'s recommendations, researchers can avoid stringent ethical review by creating embryoids without the potential to develop into a human being. It is worth pointing out that the first author, Insoo Hyun, has been recommending this strategy to researchers for several years now. For example, he advised scientists to avoid making "biologically complete but morally confusing human models" and to, instead, focus on modeling isolated developmental events that can be replicated using "purposefully incomplete …models."[22] Hence, when Yue Shao and colleagues[23] created a 3D model of post-implantation amniotic sac development using human pluripotent stem cells, Hyun praised the team for intentionally not recreating the entire post-implantation human embryo—the model lacked a primitive endoderm and trophoblast. Most importantly for Hyun, the model "did not have complete human organismal form and potential,"[24] thereby avoiding the ethical concerns a complete human embryo model might raise.

An invitation for researchers to deliberately engineer their embryoids in a manner that allows them to avoid stringent regulation need not be considered inherently objectionable (although it might incentivize duplicitousness). However, it does open these recommendations up to a familiar sort of problem, one leveled against researchers seeking alternative sources of stem cells in a debate that took place nearly fifteen year ago. Let me explain.

In the early 2000s, there was a growing research interest in stem cells, but no easy way to obtain them. Harvesting stem cells from embryos was controversial, because the extraction

required that the embryo be destroyed in the process. In 2004, however, the President's Council on Bioethics considered a proposal to extract stem cells from embryo-like entities rather than actual embryos. Doing so was possible using a procedure known as "altered nuclear transfer" (ANT). The idea, first proposed by William Hurlbut, was to use a modified version of cloning, or somatic cell nuclear transfer (SCNT). Normally, cloning involves transferring the nucleus of a somatic (body) cell to an enucleated egg (an egg that has had its own nucleus removed). Occasionally, this egg will start to develop along the same trajectory as a regular embryo, forming a culture of embryonic stem cells along the way. But to extract those stem cells is just as controversial as extracting stem cells from regular embryos, since both have the potential to develop into an organism (e.g., Dolly the sheep was created through cloning). To avoid the controversy of extracting stem cells from entities with the potential of regular embryos, Hurlbut proposed genetically altering the nucleus of the somatic donor cell so that—post transfer into the enucleated egg—it would lack the tendency to develop into an organism.

Hurlbut was himself opposed to research using actual embryos because it involved depriving an existing embryo of its potential to develop into a human being, and he saw ANT as a mechanism for scientists to program a "developmental break" into the genetic code of donor cells. As he explains:

> The crucial principle of any approach…must be the *preemptive* nature of the intervention. This process *does not* involve the creation of an embryo that is then altered to transform it into a non-embryonic entity. Rather, the proposed genetic alteration is accomplished *ab initio*, the entity is *brought into existence* with a genetic structure insufficient to generate a human embryo.[25]

By devising a process (ANT) to create mere "biological artifacts," Hurlbut believed he was giving researchers an ethical way out of their predicament. Since mere biological artifacts do not possess the teleological tendency of embryos, they cannot develop into human beings, which means that they could serve as ethically acceptable alternatives for creating stem cells.

Not everyone was sold on Hurlbut's belief. Skeptics questioned whether ANT really was producing mere biological artifacts, or whether it actually produced things akin to disabled embryos. Insoo Hyun and Kyu Won Jung summarized the skeptics' position in the following way:

> [The] deliberate act [of intervening in the manner of ANT] may strike some observers as morally equivalent to introducing a fatal genetic defect prior to the conception of what would have otherwise been a viable human embryo. Worse yet…this fatal genetic defect can be switched on and off at will. Therefore, destroying a human embryo for stem cell research is no less problematic, especially if the genetic defect can be easily reversed.[26]

The point being made here by Hyun and Jung relies on the perspectival nature of "potential." Hurlbut believed that intervening in the manner of ANT produced an entity that lacked the potential to become a fully developed organism. Hyun and Jung, on the other hand, are pointing out that the skeptic may reasonably see such intervention as no less a deprivation of potential. What Hurlbut and his ilk perceived as non-embryos (or mere biological artifacts) without the potential to become human beings, others perceived as human embryos that had been intentionally damaged or handicapped to deprive them of their potential. For the latter group, the fact that a defect had been introduced into the genome from the beginning was of little comfort. As Richard Doerflinger, from the US Catholic Bishops, explained, "any adult developing

Huntington at the age of 40 had the genetic defect *ab initio*," but that fact does not make the defect's possessor any less human or the defect any less of a harm.

I mention this slightly dated debate because its echoes resound in the recommendations made to the ISSCR by Hyun et al. According to their second and third recommendations, models that *lack the potential to develop into a human being* are exempt from mandatory ethical review required of human embryos. But given the perspectival nature of "potential," these recommendations are subject to the same types of criticisms that were raised against Hurlbut's embryo-like entities. So long as regulatory agencies rely on the "potential" of an entity to develop into an embryo to justify differences in how those entities are treated, there will always be room for impassioned skepticism. Just as interventions using ANT can be seen as interventions into something with the potential to become a human being, so too, researchers who intervene to engineer away similarities between embryoids and regular embryos are intervening on something with the potential to develop into a human embryo. That fact is simply the result of the perspectival nature of talk of an entity's "potential."

This is not the only problem haunting the use of "potential" in regulatory deliberation about research involving embryoids. In order for any *argument from potentiality*[27] regarding biological entities to work, it must be the case that some biological entities—some human cells or clumps of human cells—have a unique potential that others lack. After all, if it turned out that any human cell has the potential to develop into a human being, it would be absurd to afford only some of them special protection on that basis. And yet, as a number of authors[28] have argued, it is becoming increasingly apparent that the argument from potentiality cannot avoid such a threat. Indeed, technological advancements (especially those involving cellular reprogramming techniques) continue to support the observation that nearly any cell in a human body has the

potential to develop into a human being. Given this observation, how are we supposed to develop the idea that only certain cells have the unique potential to develop into human beings, thereby justifying the idea that they should be afforded special oversight? Without a principled answer to that question, recommendations that rely on noticing differences in cellular potential are relying on a distinction that does not mark a difference, making them vulnerable to reductio ad absurdum arguments. And my own sense is that it would be a mistake for regulatory bodies like the ISSCR to adopt such recommendations as policy.

In addition to the problems that the concept of "potential" raises for guidelines that rely on it, there is a third reason for moving away from its use when deliberating about embryoids. Even if we could rid the concept "potential" of its problems, we would still be faced with ethical quandaries involving embryoids. After all, even if an embryoid's potential to develop into a human being could be completely engineered away, it may nevertheless develop morally salient features. That is, supposing that an embyoid could never develop into a human being does nothing to alleviate worries about its developing into something of moral concern. If that is right, then lacking the potential to develop into a human being (assuming we could say what that comes to) should not be sufficient to exempt a research proposal from stringent mandatory ethical review. Consider a hypothetical: suppose a researcher is interested in modeling a discrete stage of development and engineers away the model's potential to develop into a full organism. On that supposition, modeling later stages of development allows for the possibility of developing a sentient or pain-sensing organism with no stringent mandatory ethical oversight. To prevent this problematic outcome, we should not let "potential" be the determining factor as to which models should be required to undergo stringent ethical review and which ones ought to be exempt.

Section 4: Conclusion

Different embryonic models should be treated differently based on features of the model. This is why the blanket extension of something like the 14-day rule to embryoids would be a mistake. But that concession does not support the idea that the potential of a biological entity should serve as the basis for regulatory oversight. And as I have argued, there are several reasons to steer clear of recommendations that rely on the idea of a thing's potential. So, what should serve as the basis of regulatory oversight? What ideas should our recommendations rely upon? I think we ought to follow Aach and colleagues' advice that research on embryoids ought to be restricted at the "first entry into the condition that directly raises moral concern."[29] This general principle can be applied regardless of the developmental features we take to be morally salient—whether it is the appearance of neural substrates that provide the functionality required to experience pain, as Aach and colleagues propose, or something else. That is, we can use this general principle as a deliberative signpost while we hash out the conditions that may or may not be morally significant in the development of embryoids. But whatever the morally relevant conditions end up being, what is important is that their appearance would be sufficient to trigger regulation regardless of the embryoid's potential, the way it was made, or whether it followed canonical or non-canonical embryogenesis. The fact that it has the morally relevant condition is what matters, not these other considerations.

[1] Council for International Organizations of Medical Sciences (1993). *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva: Council for International Organizations of Medical Sciences; World Medical Association Declaration of Helsinki (2000). *Ethical principles for medical research involving human subjects*. Edinburgh: World Medical Association.
[2] Matthews KR, Morali D. (2020). National human embryo and embryoid research policies: a survey of 22 top research-intensive countries. *Regenerative Medicine* 15(7): 1905-1917.
[3] US Department of Health, Education, and Welfare (DHEW) Ethics Advisory Board (1979). *Report and Conclusions: HEW Support of Research Involving Human in vitro Fertilization and Embryo Transfer*. US Government Office of Printing, Washington, DC, USA.
[4] Warnock M. (1984). *Report of the Committee of Inquiry into Human Fertilisation and Embryology*. Her Majesty's Stationery Office, London, UK.
[5] As Anne McLaren (a biologist who served on the Warnock committee) explained, "If I had to point to a stage and say "This is when I began being me," I would think it would have to be here [referring to the 14th day]" (McLaren A. Where to draw the line. *P Roy Inst*. 1984; 56: 101–121). In addition to marking the morally significant event of individuation, the 14th day seems doubly morally significant because prior to it, no structures associated with the capacity to feel pain are present. And why is pain morally significant? According to the Warnock committee, "[T]he ethics of experiments on embryos must be determined by the balance of benefit over harm, or pleasure over pain. Therefore, as long as the embryo is incapable of feeling pain, it is argued that its treatment does not weigh in the balance" (Warnock M. 1984.) In other words, if we can factor out considerations of pain or pleasure, we can simplify the moral calculus to a mere cost/benefit analysis, and insofar as research on early stage embryos is generally beneficial, the overall calculus is positive.
[6] Hyun, I, Munsie, M, Pera, M. F., Rivron, N.C., Rossant, J. (2020) Toward guidelines for Research on Human Embryo Models Formed from Stem Cells, *Stem Cell Reports* 14(2): 169-174.
[7] 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? *Nature Methods* 12(10): 917-19.
[8] Rivron, N. C., Frias-Aldeguer, J., Vrij, E. J., Boisset, J. C., Korving, J., Vivié, J., ... & Geijsen, N. (2018). Blastocyst-like structures generated solely from stem cells. *Nature*, *557*(7703), 106-111.
[9] Shao Y, Taniguchi K, Gurdziel K, Townshend RF, Xue X, Yong KMA, Sang J, Spence JR, Gumucio DL, Fu J: Selforganized amniogenesis by human pluripotent stem cells in a biomimetic implantation-like niche. Nat Mater 2017, 16:419-425
[10] Moris, N., Anlas, K., van den Brink, S.C. *et al.* An in vitro model of early anteroposterior organization during human development. *Nature* 582**,** 410–415 (2020). https://doi.org/10.1038/s41586-020-2383-9.
[11] Xue X, Sun Y, Resto-Irizarry AM, Yuan Y, Aw Yong KM, Zheng Y, Weng S, Shao Y, Chai Y, Studer L et al.: Mechanics-guided embryonic patterning of neuroectoderm tissue from human pluripotent stem cells. Nat Mater 2018, 17:633-641.
[12] Zheng, Y., Xue, X., Shao, Y. *et al.* Controlled modelling of human epiblast and amnion development using stem cells. *Nature* 573**,** 421–425 (2019). https://doi.org/10.1038/s41586-019-1535-2.
[13] Nicole Casal Moore (2019, September 12) Breakthrough stem cell platform could shed light on mysteries of early human development, retrieved 3 October 2020 from https://phys.org/news/2019-09-breakthrough-stemcell-platform-mysteries.html
[14] Rivron, N.C., Pera, M., Rossant, J., Martinez Arias A., Zernicka-Goetz, M., Fu, J., et al. (2018) Debate ethics of embryo models form stem cells. *Nature* 564(7735): 183-185, 183.
[15] These features, recall, are 1) individuation (the embryo can no longer twin) and 2) the appearance of the primitive streak (which is a precondition for the capacity to feel pain).
[16] Aach J, Lunshof J, Iyer E, Church G (2017) Addressing the ethical issues raised by synthetic human entities with embryo-like features. *eLife* 6(e20674) DOI: 10.7554/eLife.20674)
[17] Zheng et al. 2019.
[18] Warmflash, A., Sorre, B., Etoc, F., Siggia, E. D., & Brivanlou, A. H. (2014). A method to recapitulate early embryonic spatial patterning in human embryonic stem cells. *Nature Methods*, *11*(8), 847–854. http://doi.org/10.1038/nmeth.3016
[19] Hyun et al. 2020, 5.
[20] Ibid.
[21] Something else to note about the 2nd and 3rd recommendations: embryoids that do not have extraembryonic cells can be worked on without mandatory review. This allows a full embryo to be created—that is, the portion which becomes a living entity if grown in vivo—but not the portion connecting the embryo to the mother, which is

discarded at birth. Presumably, the reason this is allowed is based on the assumption that without extraembryonic cells, the embryo will have limited viability. However, given the rapid advancements in stem cell embryology, this assumption might soon prove to be naïve. Thanks to one of the reviewers for pointing this out.

[22] Hyun, I. (2017), Engineering ethics and self-organizing models of human development: opportunities and challenges. *Cell Stem Cell* 21, 718–720, 720.

[23] Y. Shao, Y. Ji, H. Fujii, K. Nagatani, A. Yamashita and H. Asama (2017), Estimation of scale and slope information for structure from motion-based 3D map, *2017 IEEE/SICE International Symposium on System Integration (SII)*, Taipei, pp. 208-213.

[24] Hyun 2017, 719.

[25] Hurlbut, W.B. (2005). Altered Nuclear Transfer as a Morally Acceptable Means for the Procurement of Human Embryonic Stem Cells. *Perspectives in Biology and Medicine 48*(2), 211-228, 226. doi:10.1353/pbm.2005.0055. emphasis in original.

[26]Hyun, I., Jung K.W. (2006), Human research cloning, embryos, and embryo-like artifacts. *The Hasting Center Report* 36(5): 34-41

[27] Stier, M., and B. Schoene-Seifert. (2013) The argument from potentiality in the embryo protection debate: Finally "depotentialized"? *American Journal of Bioethics* 13(1): 19–27.

[28] Denker H W (2014). Stem Cell Terminology and 'Synthetic' Embryos: A New Debate on Totipotency, Omnipny, and Pluripotency and How It Relates to Recent Experimental Data. *Cells Tissues Organs* 199:221-227; Devolder, K., and J. Harris (2007) The Ambiguity of the Embryo: Ethical Inconsistency in the Human Embryonic Stem Cell Debate. *Metaphilosophy* 38: 153-69; Magill, G. & Neaves, W. B. (2009) Ontological and Ethical Implications of Direct Nuclear Reprogramming. *Kennedy Institute of Ethics Journal* 19(1), 23-32. Johns Hopkins University Press. Retrieved March 24, 2018, from Project MUSE database; De Miguel-Beriain, I (2015) The ethics of stem cells revisited. *Advanced Drug Delivery Reviews* 82-83: 176-80; Testa G, Borghese L, Steinbeck JA, Brustle O (2007). Breakdown of the potentiality principle and its impact on global stem cell research. *Cell Stem Cell* 1(2): 153-6; Piotrowska, M. Avoiding the potentiality trap: thinking about the moral status of synthetic embryos. *Monash Bioeth. Rev.* (2019). https://doi.org/10.1007/s40592-019-00099-5; Sagan, A. and P. Singer (2007) The Moral Status of Stem Cells. *Metaphilosophy* 38: 264-84; Stier and Schoene-Seifert 2013.

[29] Aach et al. 2017, 8.