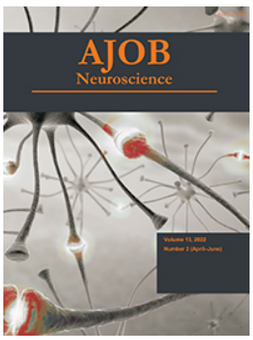

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Research Comparing iPSC-Derived Neural Organoids to Ex Vivo Brain Tissue of Postmortem Donors: Identity After Life?

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culture and/or era. It is the confrontation of ethical goals that determines their value, or invalidates them.

CONCLUSION AND PERSPECTIVES

Thus, we propose to redevelop the second school of bioethics, the "global bioethics school"—in a more optimistic perspective—also known as the "Wisconsin school," in reference to its founder, Van Rensselaer Potter, biochemist and professor at the University of Wisconsin (Potter 1971). We also think that the reintegration of a certain medical bioethics in the field will require a distinction to be made between "macrobioethics" and "microbioethics" (Durand 2007). In macrobioethics, ethical issues are identified and resolved at societal level, whereas in microbioethics, they are identified and resolved at individual level. In the face of biotechnologies, such as brain organoids, bioethics should depend more on an intellectual rigor to reason in an empirical and interdisciplinary manner, based on real scientific and clinical practices, with concrete and legitimate goals, anchored in the corresponding culture and era.

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Research Comparing iPSC-Derived Neural Organoids to Ex Vivo Brain Tissue of Postmortem Donors: Identity After Life?

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If ten of thine ten times refigured thee:
Then what could death do if thou shouldst depart,
Leaving thee living in posterity?
–Shakespeare, Sonnet 6, in Booth (2000)

Development of neural organoids using induced pluripotent stem cells (iPSCs) is a burgeoning area of biomedical research with great promise for advancing treatment of neurological and psychiatric disorders. As Sawai et al. (2022) and many others have noted, neural organoid research raises important conceptual, ethical, social, and legal questions.

A recent example brings this into sharp relief. In December 2021, a research group reported embedding iPSC-derived cortical neuronal cultures "in a simulated game world" based on *Pong*, to which the cultures responded by "playing" the game. These results,

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the group says, show that the cultures that integrated into this system "can self-organise and display intelligent and sentient behaviour" (Kagan et al. 2021, 18). The lead author of the paper and chief scientific officer of a company involved in the research further characterized the work when speaking to *New Scientist*, saying, "We think it's fair to call them cyborg brains," and "We often refer to them as living in the Matrix" (Le Page 2021).

Though this example is not our main theme, it demonstrates the urgency of further ethical reflection on applications of neural organoids research. Regardless of where the field of neuroethics comes down on such controversial applications of the technology, it is crucial to recall that scientific research is and should be answerable to the broader society in which it is embedded—both on democratic grounds (Kitcher 2011) and due to the importance of respect for persons in its various incarnations, including the necessity of consent for samples. Even ethically defensible research is therefore potentially jeopardized by an unnerved or skeptical public.

Members of our group are conducting research that could greatly advance the use of neural organoids as models to understand the pathophysiology of brain disorders and search for treatments. However, a critical step to using human-derived neural organoids as models of neural systems in the human brain is to understand to what extent the genomic landscape and the cellular interactions of neural organoids recapitulate that of actual human brain tissue. One approach to addressing this question is to compare gene expression profiles of neural organoids to those of ex vivo brain tissue from the same person. Work in progress by members of our group will achieve this by utilizing postmortem donations approved by surrogates. However, the perspectives of surrogates consenting to donations for this kind of research are understudied, particularly as they pertain to issues around identity, our focus here. Surrogates may have complex perspectives about the relation between their deceased loved one and the neural organoids they will help create.

Surrogates may view these organoids as intimately related to deceased donors due to their being (i) biologically living systems, that (ii) share the genetics of the donor, and (iii) aim to recapitulate features of the donor's brain physiology, for the purpose of (iv) comparison with a portion of the donor's actual brain. Because of the social meaning afforded to both genetics (Brodwin 2002) and the brain (Farahany et al. 2018) as crucial constituents of identity, some surrogates may well view these organoids as, in some sense or other, a continuation of a part of the donor. Indeed, qualitative research has found that lay people view brain organoids as distinct from other types of organoids precisely due to the role of the brain in identity, among other reasons (Bollinger et al. 2021; Haselager et al. 2020).

As the epigraph of our commentary attests, Anglophone culture also includes elaborate ideas and attitudes related to reproduction, including the idea of "living on" in posterity through one's children.[1] And it is certainly not alone among cultures in this respect. It is fair to wonder whether such deep-seated ideas as these may not also be extended by some to the cells in their or loved ones' bodies. In this connection, the case of Henrietta Lacks comes to mind. Lacks' daughter Deborah seems to report encountering such ideas among medical experts, and to qualifiedly endorse them herself:

> When I go to the doctor for my checkups I always say my mother was HeLa. They get all excited, tell me stuff like how her cells helped make my blood pressure medicines and antidepression pills and how all this important stuff in science happen cause of her. But they don't never explain more than just sayin, Yeah, your mother was on the moon, she been in nuclear bombs and made that polio vaccine. I really don't know how she did all that, but I guess I'm glad she did, cause that mean she helpin lots of people. I think she would like that (Skloot 2010, 9).

Alternatively, even if they do not view organoids as literal continuation of a donor, surrogates may incorporate the organoids into their conception of the broader narrative identity (Schechtman 1996) of the donor. That is, they may perceive them as potential elements of the donor's "life story." Here again Henrietta Lacks is a clear example. The incalculable value of the HeLa cell line is today conceptualized, both by members of Lacks' family and members of the public, as constituting an important part of her legacy. In other words, the story of the HeLa cell line is seen as inseparable from the story of Lacks herself—even if the cells are not conceived as literal continuations of her.

As the case of Lacks shows, considerations of narrative identity cut both ways in this context. While concerns about legacy or the addition of further, uncertain chapters to a life story might be a potential source of hesitation for some surrogates, it may also be a reason in favor of donating for others who view this research as a way for their loved one to leave an altruistic legacy by contributing to science.

These issues of identity also relate to important governance questions. In Kagan et al.'s preprint paper reporting cortical neuronal cultures playing *Pong*, some of the authors disclose potential patent interests in the

[1] See also the remaining sonnets 1–17 and the respective editor's notes in Booth (2000).

systems developed. It is important to ask whether willingness to donate samples for use in organoid research could be impacted not only by these sorts of potential applications, but also by attempts to commercialize them. And indeed, the research on laypeople's attitudes about organoids cited earlier reveals hesitation to participate in research aimed at generating profit (Bollinger et al. 2021, 1877; Haselager et al. 2020, 2356). These respondents (patients, parents of patients, and members of the public) emphasized issues of fairness, potential misuse, and the potentially corrosive effects of profit-seeking on ethics compliance.

Attitudes of the surrogate donors who make decisions in our research context may involve additional complexity due to the postmortem nature of these donations. These surrogates are highly likely, at the time donation decisions are made, to be processing the death of their loved one. We therefore suspect that identity and concomitant issues we have described (e.g., continuity, legacy) will often be at the forefront of their minds. There is a risk, therefore, that due to this sensitive context they will view patent-seeking or other means of commercialization as a claiming of ownership rights over what they understand as (in some sense) a part of their loved one, or alternatively as constituting an altruistic legacy. As one of Haselager et al. (2020, 2355)'s participants puts it, "Selling it would be disrespectful. That would mean it's treated like a material thing, although it's still a part of a person, in a way." This is but one example of how research comparing iPSC-derived neural organoids to ex vivo brain tissue may attenuate concerns already seen in existing qualitative research. These or other attitudes of surrogates may impact the decision whether to donate, and hence the research enterprise.

Of course, many surrogates may not attach any sort of personal meaning to these organoids. But the possibilities countenanced here are worth investigating empirically. In light of the dearth of existing empirical research on this topic, it will be important to conduct further qualitative work asking more in-depth questions about these themes. We suggest the issues related to identity that we have described as especially pressing. As our discussion shows, these issues potentially affect the feasibility of research and are relevant to important governance questions about this research context.

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