Human Postmortem-Derived Synthetic Neural Models: Identity after Life?

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The difficulty in obtaining brain tissue from living individuals has limited the understanding of cellular processes associated with brain function. Advances in induced pluripotent stem cell (iPSC) development and differentiation into neural organoids (i.e., synthetic neural models (SNM)) provide a new approach to study cellular networks in brain. However, the degree of fidelity of iPSC-derived SNMs to the personalized cellular environments and gene network interactions they aim to model is unknown. One approach to addressing this question is to compare cellular and gene network profiles of SNMs to those of ex-vivo brain tissue provided by the same donor. To achieve this, work in progress by members of our group utilizes postmortem donations approved by surrogates. Using an iPSC-derived SNM differentiation protocol starting from fibroblasts collected from skin biopsies, we performed a comprehensive functional analysis of the gene expression processes across transformation and differentiation to SNMs, and compared the SNM gene network profiles to those from isogenic human brain.

This work has important ethical, social, legal, and policy dimensions. Our group will address these matters by examining how SNMs: 1) may impact definitions of the boundaries of life and death, 2) whether these have moral status and symbolic significance, 3) how these may be seen as an extension of the donor's identity, 4) what are acceptable research goals, processes, and limits, 5) what drives decisions to donate, and 6) any unexpected considerations that emerge during the study.

There is a dearth of research on stakeholder perspectives regarding neural organoids. The viability and shape of this research may be impacted by views of both SNM researchers performing the scientific work and donor next of kin who make the decision whether to donate samples. These next of kin donor surrogates may view SNMs as intimately related to 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. Contemporary Western culture affords a great deal of meaning to both genetics and the brain in relation to identity, and considerations of identity, life narrative, and legacy are likely to be at the forefront of surrogate decision-makers' minds as they process the recent death of a loved one. To maximize the benefits and minimize any potential harms of this research, it is important to identify and address any concerns key stakeholders may have and whether there are significant discordances between next of kin and researchers that could impact the viability of this research and how these may be addressed.

Understanding the extent to which SNM recapitulate the brain tissue from the donor from which they are derived will improve understanding of brain function, and allow the creation of neuronal models to test hypotheses regarding brain disorders. The collaboration between scientists and ethicists will allow comprehensive examination of ethical and social considerations and development of ethically-sound practices to inform current and future research.