An Ethical Consideration of Organoid Technology

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Introduction

Organoids are emerging powerful technology systems that mimic the complexity of organs and provide an opportunity to accurately model human biology (Corrò et al., 2020). These three- dimensional (3D) systems were first expressed from intestinal stem cells and were shown to form 3D intestinal organoids by Sato et. Al in 2009. From there, organoids continued to evolve through the establishment of this technology in other biological systems. Organ-on-chips (OoCs) are 3D microdevices that model the structure, functionality, and behavior of specific tissues or organs using human cells. OoCs serve as a branch under the organoid technology field but have an added device fabrication component of incorporating microfabricated fluidic channels and microelectronics (Thakar et al., 2023). OoCs devices are currently used to replicate human organ functions in a controlled laboratory setting for drug testing and disease research.

OoCs recreate the physiology of the human body as they contain networks of hair-fine microchannels for manipulating minute volumes and aim to surpass current *in vitro* models in accuracy and complexity. The organ serves to be miniature tissues grown to reside in microfluidic chips, which can recapitulate one or more tissue-specific functions (Leung et al., 2022). The goal of the Technical Capstone project is to contribute to the development of OoCs in a clinical setting by enhancing the accuracy of bioluminescent monitoring instrumentation in the microfluidic device. Bioluminescence is the production and emission of light by living organisms, typically because of a chemical reaction involving a light-emitting molecule called luciferin and an enzyme called luciferase, which can be added to any tissue of interest (Adams & Miller, 2020). Organ models often use bioluminescence analysis, via standalone incubating luminometers, due to its high signal-to-noise-ratio metrics, simple equipment integration, and

broad applicability. At the conclusion of this project, the Capstone team will have developed an integrated OoC system for detection of bioluminescence for circadian rhythm analysis.

The STS research project will focus on the ethical consideration of organoid technology use, as the field is continuously changing and growing faster than regulations can manage. Organoid ownership and individual rights of organ donors must be considered when developing these products for commercialization. Reviewing the ideas of identification approaches in organoid use, commercialization considerations, and informed consent models of the OoCs, like what the technical project is developing, will help create an ethical framework to navigate this rapidly evolving landscape. The STS research project addresses emerging ethical challenges associated with organoid technology, offering a crucial outline for its responsible progression. In this paper, I argue that my approach to this problem will draw attention to the urgent need for ethical guidance in the rapidly advancing field of organoid technology.

Literature Review

Lewis and Holm discuss the autonomy of organoids and the limits of donor consent in current models, which affect the development of organoid technology and specifically, organoid biobanks which hold deposits of organoid cell lines and tissues for research. Blanket consent, opt-out, broad consent, and specific consent represent distinct approaches to utilization of organoids in research. Specific consent involves donors agreeing to a particular research project, while blanket consent and opt-out entail open-ended consent for future tissue use. Broad consent falls in between, involving consent for a broader category of research without specific details. Different consent models, such as specific, tiered, opt-in, and dynamic, typically require explicit participant consent for each scientific sample reuse. In contrast, broad, blanket, governance

consent, and opt-out models allow samples to be reused for various research projects without recontacting the donor or providing specific project information (de Jongh et al., 2022). Dynamic consent enables donors to switch between consent models, allowing them to benefit from different approaches depending on the situation, providing flexibility and control. The various informed consent models proposed for organoid research offer diverse approaches to balance donor control and the scope of future research use, catering to different ethical considerations and levels of participant engagement (Lewis & Holm, 2022).

Organoid transplantation, though still in a preclinical phase, is based on established principles of stem cell treatments, some already in human trials for conditions like stroke and Parkinson's disease. However, ethical concerns arise regarding organoid trials, as they lack human in vivo data and pose unforeseen risks. Additionally, organoid technology may impact moral actions and quality of life in unforeseen ways. Linking organoids to *in vivo* organs might involve creating chimeras, single organisms composed of cells with more than one distinct genotype, raising ethical dilemmas. Studies indicate that some donors are hesitant about certain sensitive applications of organoids, such as chimeric research. Similarly, precision medicine research using organoids aims to connect donors' biospecimen with health, genetic, and digital data to create personalized models for disease and treatment. Donors may worry about how their biospecimen are used, particularly for uncovering unexpected findings not initially anticipated or planned for during consent (Lewis & Holm, 2022).

de Jongh et al. discuss the difficulties of consent in organoid use and the commercial value of organoids, which are on the rise, attracting both public and private stakeholders, including pharmaceutical companies. The challenges of implementing an informed consent model in organoid research stems from the rapid evolution of research and technology makes it

difficult to predict and describe potential future uses and storage of donor samples. Secondly, the involvement of multiple parties (researchers, companies, patients, donors) complicates the protection of their values and interests. Thirdly, donors may perceive organoid models differently from cell lines, affecting the complexity of the consent process. Lastly, the use of donor tissue for sensitive organoid sub-types, such as brain organoids, raises ethical concerns while link between the donor and the sample is clinically relevant but complicates privacy protection. Addressing these challenges is essential for the ethical progression of organoid technology (Shariati et al., 2021).

The commercialization of organoids also presents technologies become potentially patentable, third parties, aside from donors, might gain property rights over them. This profit potential has the potential to drive scientific advancements, though it also raises concerns among patients about excessive commercial involvement. Making a profit from organoids raises concerns among patients, donors, and stakeholders as it creates tension between the altruistic motives of donors and the monetary interests of commercial businesses. Donors provide tissue without personal benefit while commercial parties profit from organoids through property rights and sales. Therefore, fair benefit distribution must be developed address these concerns among commercial parties, researchers, donors, and other stakeholders. Profiting from patient-derived tissues is seen as ethically unfair due to their vulnerable position (de Jongh et al., 2022).

Organoid transplantation and precision medicine research using organoids raise ethical concerns due to the lack of human in vivo data, potential unforeseen risks, and impacts on moral actions and quality of life. Donors may be apprehensive about how their biospecimen are used, especially regarding unexpected findings not initially considered during consent. Therefore, there is room for more autonomy in organoid research consent models to address these concerns and

ensure donor agency and ethical oversight. On the other hand, given these informed consent and commercialization concerns, it is imperative to revisit and refine current policies to create a more balanced approach that respects both the potential for scientific advancements and the ethical considerations tied to organoid technology development (de Jongh et al., 2022).

The discussion by Lewis and Holm on organoid autonomy and consent models directly relates to de Jongh et al.'s examination of the challenges of consent in organoid research and the commercialization of organoids. Both sources highlight the complexity of informed consent models in balancing donor control and ethical considerations amidst rapid technological advancements and commercial interests, emphasizing the need for nuanced approaches to ensure ethical progression and fair benefit distribution in organoid research. This paper's discussion aims to use an STS conceptual framework to explore the intersection of technological advancement, ethical considerations, and commercial interests in organoid research, guided by the insights provided by Lewis and Holm and de Jongh et al. It will contribute to the ongoing dialogue surrounding the responsible use of organoids by proposing strategies to enhance donor autonomy, ethical oversight, and equitable benefit distribution in this rapidly evolving field.

Conceptual Framework

The ethical framework of responsible research and innovation is the idea of promoting social good in technological development through the anticipation of future issues. This concept is crucial to the conversation of organoid development, as the technology is newer, as it seeks to respond to ethical issues that arise in this industry. As explained by Stilgoe et al., the key to applying this framework is to understand the responsible innovation, beyond aspiration and moral values, and the deficits of the current approaches to innovation governance. Responsible innovation goes beyond considering what products are wanted or not wanted from science and

technology. It also involves reflecting on the purpose of products and prompts thinking about the future and the challenges technology will address. To innovate responsibly involves a collective commitment to anticipate, reflect, deliberate, and respond to the potential impacts and implications of scientific and technological advancements. The goal is to build "reflexive capital" that informs decisions about innovation trajectories, allowing for ethical, sustainable, and socially desirable outcomes. Responsible innovation requires institutional embedding and challenges traditional approaches to science and innovation, but it also aims to enhance creativity and curiosity rather than stifle them (Stilgoe et al., 2013).

Applying the framework of responsible research and innovation will provide a structured approach to analyzing the ethical dimensions of organoid development as discussed by Lewis and Holm and de Jongh et al. This framework encourages anticipating future ethical issues, such as those related to donor consent, commercialization, and the impacts of technological advancements, and reflects on the purpose of organoid products in addressing societal needs. By collectively deliberating on these issues, stakeholders can work towards fostering ethical, sustainable, and socially desirable outcomes in organoid research and development. This approach involves not only considering the immediate benefits and risks but also contemplating the long-term implications of organoid technology, thereby promoting responsible innovation that balances scientific progress with ethical considerations.

Methodology

To begin creating a framework on the ethical consideration of organoid technology development, a review of existing literature on organoid technology and its applications is needed. This includes a review of secondary, qualitative data to summarize the current ethical standings of the organoid technology industry. Similarly, an analysis of the ethical frameworks

and guidelines that currently exist in the field will be used to create ethical guidelines for the responsible advancement of organoid technology. Specifically, studying organoid development policy of major corporations and governments will be essential in understanding frameworks for privacy concerns and commercialization of this technology. Lastly, case studies from various patients and donor perspectives are required to include concerns that real stakeholders face as the field advances. This comprehensive approach will be facilitated through a systematic literature review of the sources as previously discussed. Furthermore, viewing the literature through the lens of responsible research and innovation will help shape this conversation to promote advancements in the field that are not only scientifically sound but also socially responsible.

Understanding the complexities of organoid technology is vital for stakeholders, shaping responsible progress and ethics in its development and use by researchers, donors, companies, and users. A review of existing policies can identify potential areas for improvement. Similarly, engaging with the perspectives of diverse stakeholders will ensure the framework accounts for their concerns and needs. Given these informed consent and commercialization concerns, it is imperative to revisit and refine current policies to create a more balanced approach that respects both the potential for scientific advancements and the ethical considerations tied to organoid technology development (de Jongh et al., 2022). By carefully reviewing current policies and understanding the gaps in regulation of this technology, a framework can be created to responsible and transparent development, addressing potential risks, and promoting the ethical use of these innovative advancements in healthcare and research.

Discussion

Stakeholders of Organoid Technology

To understand the breadth of ethical issues regarding the organoid technology field, it is important to discuss the stakeholders who are often directing the development and implementation of this technology. These stakeholders encompass a wide array of groups, ranging from scientists and researchers to policymakers, healthcare providers, patients, and the public.

The stakeholders driving advancement of this industry includes both public and private groups, including researchers and businesses, such as pharmaceuticals. Profit generation of organoids by commercial parties could lead to advancements in science, which is hopeful for patients and professionals. On the other hand, patients should be labeled as the key stakeholders. Consent models prioritize patient preferences and values, empowering them as active participants rather than passive donors. They engage patients in an ongoing communicative process, granting them control. Policymakers also serve as crucial stakeholders in the organoid industry, shaping regulatory frameworks and guidelines to ensure ethical standards, safety, and innovation. Similarly, healthcare workers play a vital role as stakeholders in the organoid industry, utilizing these technologies for research, diagnosis, and personalized treatment strategies. Their expertise and feedback contribute to the development and implementation of organoid-based medical advancements, ultimately benefiting patient care.

Workshops led by Ravn et al. represent current public perceptions of the organoid technology industry, which seems to be a driving factor determining policy that defines this research. Participants tend to endorse the use of organoid technologies provided when there is assurance of responsible governance, ethical oversight, and robust informed consent protocols. However, a wide array of apprehensions is acknowledged, particularly regarding issues such as commercialization, equitable healthcare access, and the specific case of cerebral organoids. As

the organoid technology field continues to evolve, fostering transparency and accountability among stakeholders will be essential in navigating the ethical complexities and ensuring that advancements serve the collective interests of patients, professionals, and society (Ravn et al., 2023).

Benefits of Organoid Technology Use

As discussed with the selected sources, there are many benefits to using organoid technology. Notably, organoids often serve as great models for applications spanning from basic developmental/stem cell research to personalized medicine. Organoids, particularly human-derived ones, offer a promising avenue for studying infectious diseases due to their ability to model human biology without interspecies differences encountered in animal models. Furthermore, the presence of multiple cell types within organoids and the capacity to manipulate media composition enable researchers to closely mimic tissue environments and investigate host-pathogen interactions. These attributes make organoids a valuable tool for dissecting the mechanisms of infectious diseases and developing targeted interventions. Additionally, organoid technology presents an asset to the drug development industry by providing a platform for testing drug efficacy and toxicity in a more physiologically relevant context, potentially expediting the drug discovery process and reducing reliance on animal models (Yang et al., 2020). In the context of the responsible research and innovation framework, this technology promotes ethical practices by offering a more humane and accurate alternative to animal testing, aligning with societal values and regulatory standards while advancing medical progress.

Mouse-derived organoids blend the strengths of mouse genetics with the flexibility of 3D culture techniques, offering a potent tool for genomic research in a more physiologically relevant environment. Additionally, the ease of manipulating the stem cell niche components enables

researchers to investigate the role of signaling pathways in stem cell maintenance or differentiation. After cell cultures are established, genomic engineering using human organoids can help trace cell lines, such as cancer cells. This application of organoid technology seeks to foster advancements in understanding more about the origins of human disease and genetic information. This use of organoid technology also aligns with the responsible research and innovation framework as it prioritizes transparency of where cell lines are derived from and how they are traced. Similarly, the use of diverse cell lines that develop the organoids allows for this research to be generalized to a greater population (Artegiani and Clevers, 2018).

Ethical Limitations of Organoid Use

Organoids model the development and maintenance of a human organ; they have the potential to revolutionize biomedical research and change the drug discovery process. Patient-derived organoids offer possibilities to mimic pathologies of human genetic disorders and develop personalized treatment. The rise of organoid models significantly influences the ethical discourse surrounding animal experimentation. While sacrificing animals for research is still common, it is still seen as ethically contentious. Organoid technology may be viewed as the long-awaited alternative to animal testing. Current limitations of organoid models include variable shape and lack of defined architecture, which may be addressed in the future with bioengineered scaffolds. Additionally, absence of blood vessels and immune cells in most protocols hinder organoid size, complexity, and immune system interactions. Within the framework of responsible research and innovation, this technology poses ethical promise to minimize reliance on animal experimentation while advancing biomedical research. The choice between organoids and animal experimentation requires ongoing justification, with the need for animal studies evaluated case-by-case. Legal frameworks can develop to prioritize reducing,

refining, and replacing animal experiments with alternatives such as organoid models. Funding agencies and research institutes could ensure that experiments minimize animal harm through subsidizing this technology through grants.

Organoids, especially those derived from pluripotent stem cells, also involve the utilization of research material from human embryos and fetuses. Live-imaging experiments on human fetal organoids have resulted in crucial insights into brain development. In terms of patient ownership, as this topic also represents a source of ethical contention. Using Lewis and Holm's discussion on organoid autonomy and consent models, it is important to consider the role of the autonomy of fetuses and their ownership when using these organoids in a wide scale. On the other hand, organoids derived from fetus tissue could present a moral alternative to using human fetus tissue in research, as it may avoid the need for an increased sample size if many organoid models can be developed from one source. Again, this discussion presents two sides of the concept of responsible research and innovation. The use of organoid models from humans requires say from said source, yet it could provide an avenue to developing a more ethical practice of understanding human gestational development.

The creation of organoids from adult stem cells introduces unique ethical considerations, particularly concerning the establishment and operation of living biobanks to ensure a consistent supply. This has sparked an ongoing ethical debate surrounding the governance and practices of biobanking. Despite these challenges, organoid biobanking holds significant promise for advancing scientific research, precision medicine, and regenerative therapies. The ethical complexities of organoid biobanking reflect the intersection of various ethical discussions within this evolving field. For organoid biobanking, complete de-identification may not always be optimal as it can disconnect samples from patient history and limit potential benefits for biobank

donors. Therefore, the use of human tissue for organoid biobanking requires attention to the patient consent process such as discussed by discussed by Lewis and Holm and de Jongh et al. As proposed, often the broad consent for governance or dynamic consent can be applied while adhering to the idea of responsible research and innovation. In these approaches, donors are informed about the governance structure of the biobank, including ethics oversight, privacy policies, collaboration, data management, communication, and withdrawal procedures. This consent model empowers donors to make autonomous decisions while facilitating the broad use of their materials by multiple researchers. Implementing this consent approach necessitates a robust and adaptable governance framework that safeguards the interests of all stakeholders involved, beyond solely scientific requirements.

As this field is further developed, empirical studies and workshops with various groups of stakeholders and donors are crucial to understanding donors' perspectives on organoids, their interests, and how they perceive organoid donation compared to other tissue research donations. These studies will inform whether a distinct consent and oversight approach is required for organoid generation, especially considering the expected rise in commercial applications of organoid models in the coming years (Bredenoord et al., 2017).

Conclusion

The utilization of organoid technology offers a myriad of benefits across biomedical research, ranging from personalized medicine to drug development, genomic research, and regenerative therapies. These advancements align with the principles of responsible research and innovation, aiming to minimize reliance on ethically contentious practices such as animal experimentation while advancing medical progress. However, the ethical landscape surrounding organoid technology is complex, necessitating ongoing interdisciplinary dialogue to address

issues such as patient consent, biobanking governance, and the balance between scientific advancement and ethical considerations.

Organoids are emerging as valuable model systems alongside existing animal and cell-based models for research, though they are unlikely to completely replace animal experiments or studies involving human embryos and fetuses. By engaging stakeholders from diverse backgrounds and incorporating transparent consent models, we can navigate these challenges and ensure the ethical and responsible advancement of organoid technology for the betterment of science and society. Setting up policy and guidance in responsibly innovating this technology will benefit not only dealing with the organoid technology industry but provide a framework for future innovations that also provide to be ethically contentious.

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