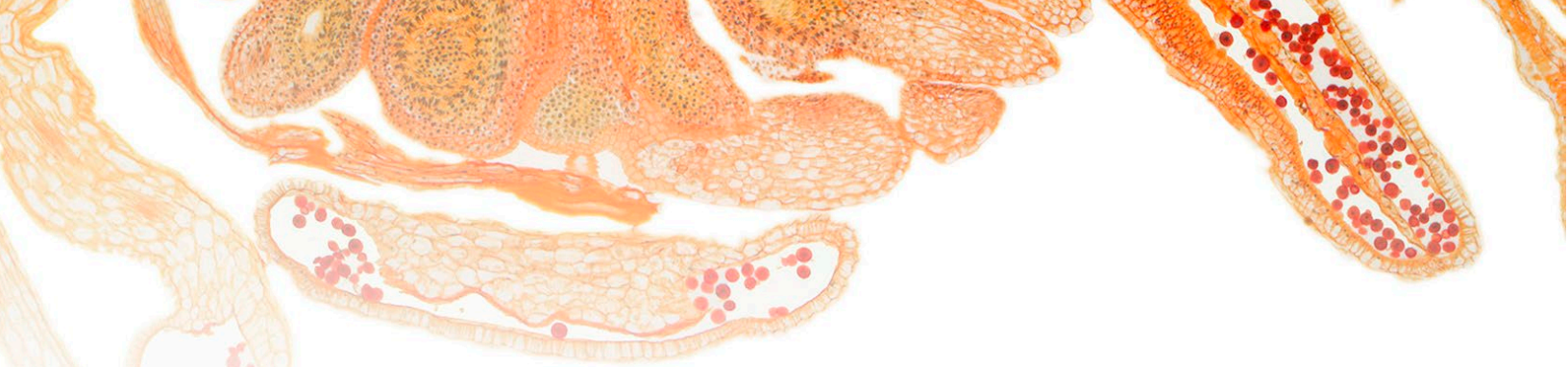

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POLICY FORUM

Which Concepts Are Key to Transitioning From Nonhuman Animal Models to Engineered Microphysiological Systems in Biomedical Research?

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Abstract

A transition from nonhuman animal models to engineered microphysiological systems (MPS), such as organoids and organ-on-a-chip technologies, would signal a paradigm shift in biomedical research. Despite MPS' potential to more accurately model human physiology, reduce high failure rates of drugs in clinical trials, and limit unnecessary animal use, widespread adoption is hampered by public opinion and lack of scalability, standardization, and current regulatory uptake. This article suggests how 5 key concepts (awareness, access, education, application, and rewards) could help address these barriers. These concepts are part of a framework that underscores a need to integrate MPS into mainstream biomedical research and to better promote ethical responsibility for the means of biomedical innovation.

Paradigm Shift in Research Modeling

We are approaching a tipping point in the burgeoning field of engineered microphysiological systems (MPS) as alternatives to nonhuman animal research models. MPS are in vitro platforms that mimic aspects of human and nonhuman animal physiology using tissue- or organ-specific cells. Microfluidic organ-on-a-chip (organ chip) technologies and organoids are MPS that have shown significant promise in research and drug development, as they continue to demonstrate physiological relevance. It has long been recognized that the physiological systems of nonhuman animal models do not sufficiently resemble those of humans, and, consequently, an estimated 95% of drugs fail in human clinical trials.[1] Humans may also be deprived of effective drugs that never reach clinical trials because they failed prematurely in animal models. Nevertheless, animal models are the de facto use case for validation studies.

Nonhuman animal models have remained the universal standard in translational research for several reasons: (1) traditional in vitro models cannot sufficiently replicate complex and dynamic human physiological systems; (2) animals can be genetically engineered to replicate various disease states; and (3) many necessary scientific experiments cannot be ethically conducted on human subjects. For decades, the scientific community has also debated whether such experiments can be ethically

conducted in nonhuman animal subjects.[2] This moral dilemma is compounded by the failures of nonhuman animal model systems in translational science that are widely recognized by academia and industry.[3] The transition towards MPS is thus grounded in both ethics and practicality. It highlights the empirical and normative challenges of the current animal research model paradigm and pushes us to consider our obligations to science, humanity, and other animal species.

Engineered Microphysiological Systems

The transition toward commercialization of MPS is underway but faces challenges in widespread adoption. Technical limitations, validation and standardization of MPS models, and regulatory hurdles are primary blockers. In December 2022, the bipartisan-supported FDA Modernization Act 2.0 removed the long-standing requirement for drug developers to conduct animal toxicity testing of novel drugs before human trials.[4] Although the act is a significant step forward in fostering the adoption of MPS, it does not mandate the reduction or replacement of animal use, nor does it explicitly incentivize the use of MPS. US regulatory agencies like the US Food and Drug Administration (FDA) have long-standing protocols that are based on animal testing. Incorporating MPS data in drug approval processes requires extensive historical evidence, which presents a barrier to rapid adoption of these technologies.

Importantly, MPS support the widely used "3 *R*" framework for nonhuman animal research. The 3 *R*'s represent the principles of replacement, reduction, and refinement—ie, the replacement of nonhuman animals in research with alternative tools, the reduction of animal use required to meet scientific aims, and the refinement of animal welfare conditions to alleviate or eliminate animal pain and distress. MPS make the principles of replacement and reduction more achievable.

As mentioned above, organ chips and organoids are MPS that offer advanced alternatives to traditional animal models. Organ chips, microfluidic devices that mimic whole-organ functions, can be linked to form multi-organ or body-on-a-chip systems, simulating organ interactions and fluid dynamics seen in vivo. While particularly effective in pharmacokinetic studies, they cannot fully capture an organ's complexity and require custom fit-for-purpose designs, limiting their scalability.[5] Organoids, on the other hand, are 3-dimensional, stem cell-derived tissues that model organ structure and function and are useful in organ development studies, disease modeling, and preclinical drug development. However, organoids have short lifespans and a lack of vascularization that limits their ability to recapitulate the in vivo transport of oxygen, nutrients, and chemicals to living tissues.[6] Despite these limitations, the accuracy of both technologies in certain research areas has been shown to be equivalent to or surpass that of nonhuman animal models, with ongoing reviews indicating their growing efficacy in clinical research.[7]

Given these technologies' promise, it is important to view regulatory and scientific challenges in context. When juxtaposed to the troubling physiological irrelevance of animal models in drug development, MPS draw our attention to critical ethical questions. Should we allow long-standing frameworks to impede scientific progress? Do scientific researchers have a moral responsibility to change course when confronted with the failure of existing systems? Is it ethically permissible to ignore the failures of standard animal models and deprive people of future solutions by restricting the development of lifesaving therapeutics facilitated by MPS?

Now is the time to address these ethical questions and practical considerations. MPS present us with novel in vitro human research opportunities. Failure to consistently replicate preclinical trial results is estimated to cost $28 billion USD per year, with a drug-to-market failure rate of 90%.[8,9] The most common causes cited for these failures are toxicity and inefficacy, both of which may be better addressed by MPS than by animal models. In light of these deficiencies—and following a global pandemic that underscored the importance of rapid medical innovation—it is clear that we ought to urgently pursue the transition away from animal models toward viable MPS alternatives.

Advancing the Transition to MPS

Many questions remain about how to deploy ethics in constructive ways that simultaneously advance state-of-the-art research and serve as the guardrails required in any medical field, given the tensions that exist between science, industry, and regulatory policy. Special attention should be paid to the multidisciplinary nature of MPS, the variety of stakeholders, and the basic human psychological aversion to paradigm-shifting change. We can consider how ethics might be practically applied to advance the transition from animal models to MPS using a framework comprising 5 actionable pillars: (1) awareness, (2) access, (3) education, (4) application, and (5) rewards.

Awareness. The field of MPS is multidisciplinary and sits at the nexus of science, engineering, and technology. Its numerous stakeholders include researchers, clinicians, regulators, journals, teachers, students, investors, and the general public. As a primary step in advancing the transition to MPS, all stakeholders have an ethical obligation to become aware of this existing technology because stakeholders are human first, and humans have a collective duty to support flourishing––the Aristotelian ideal of a holistically well-lived life.[10] This flourishing includes the pursuit of new, transformative knowledge that improves the lived experiences of human beings and, it can be argued, the lives of nonhuman beings. It is equally important to ensure that the pros and cons of MPS are clearly communicated so that people have a holistic rather than narrow awareness of their potential. Although MPS technologies have limited scalability because they are fit-for-purpose, animal models have clear technical, economic, and ethical limitations. All stakeholders need to be aware of those limitations as experts seek to overcome them with new options.

Access. The need for sufficient access to transformative technology is underpinned by cornerstone ethical principles such as equity, inclusion, justice, and fairness. It is broadly applicable to all MPS stakeholders, although the type of access required varies by role. Patients and clinicians require access to information about the treatments developed via MPS for decision-making, while academic institutions require access to the technology to conduct training and research. Access is also mediated by economic considerations. Industrial and academic pricing differs, as does the value MPS provide to academia and industry, where they can be used to narrowly or broadly advance medical research. Moreover, access is tied to different sets of responsibilities. The government should be responsible for training people who conduct grant reviews to accept nonhuman animal models; the FDA Modernization Act 2.0 paved the way for the actualization of this responsibility. Journals have a responsibility to promote scientific research by sharing transformative knowledge. Via the peer review process, journals function as gatekeepers to both legitimize scientific research and guide its future direction.[11] MPS access may be diminished when reviewers continue to require animal validation studies despite their well-known failures in translational research.[12] Without

sufficient access to MPS by regulators, grant reviewers, researchers, students, and other stakeholders, few will truly understand or seek to leverage the technologies' capabilities.

Education. A fundamental challenge to the widespread adoption of MPS is the basic human psychological resistance to change. Change is perceived as a threat, and, in response, the brain signals the release of stress hormones.[13] We are hardwired to avoid change as an evolutionarily protective mechanism. Like neural circuitry, the pathways of animal models in biomedical research are hardwired into scientific processes and reinforced the more they are used. However, like new neural connections, new scientific pathways can be developed through training and education. Stakeholders in the biomedical sciences, academia, and government have a social responsibility to explore new technologies that improve medical outcomes, even if it means accepting the fact that the methods they currently use are both subpar and unethical. Ethics both inform and evolve in response to technological advancement. Normalizing MPS through education can increase institutional uptake, support a new generation of researchers, and move science closer to realizing goals that benefit both humans and nonhuman animals.

Application. Ethics questions arising from the application of MPS are vast and worthy of a separate discussion. At a high level, protective guidelines concerning emergent medical technologies, such as genetic engineering of DNA and in vitro fertilization, have historical precedent.[14,15] MPS will remain bound by the ethical guardrails of the emergent technologies that came before it, and its evolution will generate new ethical challenges. Already, human sperm has been put on cervical organ chips, neuronal cells have been used in brain chips, and brain organoids can achieve some functionality.[16,17,18] While replicating fertility and brain function is technically plausible, these incomplete recapitulations require further ethical consideration. As the application of MPS evolve, ethical and regulatory guidance must evolve alongside them in real time rather than reactively and in retrospect.

Rewards. Ethical incentives might motivate stakeholders to take the risk of replacing animal models with MPS. Researchers working on toxicology studies, journal reviewers, and FDA representatives have historically relied on animal models, and, despite their well-documented deficiencies, there has been little incentive to move away from them. Yet there is historical precedent for the involvement of institutions in fostering technological adoption. As an example, the rise of transgenic mice in the 1980s was supported by Harvard taking advantage of changes in patent law and was promulgated by scientific journals.[19] It would be ethically permissible to do the same for MPS.

While there are grants supporting MPS and recent legislation allows for MPS adoption in drug development,[4,20] additional incentives are required to trigger a key tipping point in industry and academia's transition to MPS. One suggestion is to extend patents for the first companies to use MPS to bring a drug to market. The patent extension provides ample economic incentive and, if supported equitably with grant dollars, could facilitate a moonshot MPS race that triggers a new wave of research, development, and investment. Establishing a government-subsidized consortium of MPS-interested companies is another option; industry, the government, and the public can all benefit from advancements facilitated by MPS. Some pharmaceutical companies are already self-selecting subgroups of people open to taking risks on new technologies and creating programs to explore MPS.[21] However, such initiatives are expensive and may

not be equally available to all industry participants. In this case, a subsidized consortium could help distribute opportunities among a diverse set of participants.

Conclusion

Despite technical, regulatory, and educational hurdles, the need to transition away from animal models and adopt more accurate, humane, and efficient research models like MPS is clear. The described framework provides a lens through which to examine the ethical, practical, and scientific nuances of this shift, but it is important to supplement and build upon it. The journey toward fully integrating MPS into mainstream research and overcoming existing ethical tensions will be complex and multifaceted, requiring concerted efforts across disciplines. Nevertheless, the promise of MPS to advance clinical science, reduce unnecessary animal suffering, and unlock new avenues in drug development and disease understanding makes this journey not just necessary but essential for the future of ethical and effective biomedical research.

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