The Future of Miniaturised Organs in Drug Development and Testing

Timothy S. Chisholm
Department of Chemistry
University of Cambridge

ABSTRACT

Drug development is time consuming and expensive, partly due to the difficulty of determining the safety and effectiveness of drugs in humans. To improve this process, there is a demand for models appropriate for studying the biological effects of drugs early in their development. This article considers miniaturised organ technology to evaluate the safety and efficacy of medicines and reduce our dependence on animal testing. Testing drugs on miniaturised organs could also help account for systematic biases in clinical trial populations. However, ethical concerns exist including patient consent and the anonymisation of tissue donations. This article considers these key concerns and provides policy recommendations for the ethical and responsible use of miniaturised organ technology.

SCIENCE ⇒ POLICY

Miniaturised organs grown from human tissue are showing promise as tools to test drug safety and efficacy. This technology could reduce the need for animal testing and help account for systemic biases in clinical trials. Policies are needed to ensure this technology is adopted responsibly, and to address ethical concerns around patient consent and donor anonymisation.

Keywords Miniaturised organs · organoids · clinical trials · drug development

Aim and Objectives

The aim of this article is to outline applications of testing drugs on miniaturised organs and to discuss the implications this technology has for policy. The benefits of this technology in drug development and clinical trials will be evaluated, followed by a discussion of related ethical concerns. Policy recommendations will then be made to address these concerns and promote a positive impact of this technology.

Scientific Background

Drug development is a lengthy and expensive process (Figure 1) [1, 2]. Candidate drugs are
discovered and developed, then undergo animal testing in pre-clinical trials to investigate safety and the effects of the drug on a living organism. If these results are promising, the safety and efficacy of the drug is tested with human subjects in clinical trials before regulatory approval.

Advances in chemistry and biology have improved the design and synthesis of medicines. However, testing the safety and efficacy of new drugs remains challenging. Testing drugs in animals has ethical considerations and it imprecisely models how the drug will affect humans [1, 2]. Additionally, drugs can have different efficacies and safety profiles in different people [3–11].

These issues may be addressed with the help of organoids and organs-on-chips, which are simplified, miniaturised humans organs (Figure 2) [12]. To grow organoids, adult human cells are reprogrammed into a stem cell, a type of progenitor cell that can develop into different cell types (Figure 2a). Stem cells are embedded in a gel where they divide and specialise into specific cell types, producing an organoid [13, 14]. Organs-on-chips are grown with a different approach. In the simplest form, a narrow tube containing a single cell type is used [15–17]. More complex systems can be fabricated with multiple types of cells separated by porous membranes (Figure 2b). Fluid can be pumped through the tubing for several purposes, such as mimicking blood flow.

One application of miniaturised organs is to test the safety and efficacy of drugs [15–20]. A limitation of animal models for drug testing is the difference between human and test animal biology, especially liver and kidney physiology [21–25]. Drugs are processed by the liver, producing by-products which are excreted by the kidneys into urine. Differences in human and test animal physiology mean that drugs may be processed and excreted differently [23, 25]. For example, toxic by-products may be produced and accumulate in humans but not some animals [22, 27].

As miniaturised organs are grown from human tissue, they can more closely mirror parts of human physiology than test animals [28, 30]. Testing medicines on miniaturised organs could therefore provide safety and efficacy data that animal models cannot [28, 32, 35, 41]. However, animal models remain the only method to study drugs in living organisms with fully grown, interconnected organ systems before human trials. Both testing methods therefore have their advantages. Miniaturised organ testing could be used to screen drugs prior to animal testing and, as the technology advances, could further complement and replace aspects of animal testing [13, 16, 19, 28, 55, 42]. The ideal outcome, which policy should support, is more efficient drug development that delivers safer and more effective drug candidates with reduced animal use.

Policy Implications

Policies and regulations that outline how testing drugs on miniaturised organs can be considered in the drug development process are required. Miniaturised organ testing may identify safety or efficacy concerns that would remain unidentified until animal or human trials [14, 15, 42, 43]. This approach would address a demand for the reduction of animal testing by medical and regulatory agencies, including the European Medicines Agency (EMA) [29, 30, 44–48]. However, uncertainty regarding how these technologies will be considered by regulators is hampering the adoption of miniaturised organ testing. The EMA states: “... the uptake of these newer models [miniaturised organ testing] in marketing authorisation submissions has not been high ... One reason for hesitancy may be concerns ... that use of such New Approach Methodologies (NAMs) will not be acceptable to regulators and will thus stall approvals ... Encouragement of these techniques is therefore needed” [46].

In addition to this apparent lack of clear regulatory guidelines, the EMA suggests that a lack of knowledge of such models and high implementation costs also play a role. If regulators outline how they would consider miniaturised organ testing, this could improve the confidence of pharmaceutical companies in this technology, increasing uptake.

Miniaturised organ testing can also help account for biases in clinical trials, which generally over-represent men of European descent [8, 5]. While recent trials exhibit an improved gender balance, many groups remain underrepresented. The safety and efficacy of medicines are therefore not
Figure 1: **Drug Discovery and Development Pipeline.** Overview of a traditional drug discovery and development pipeline with approximate values for the time taken and the number of chemicals at each stage. Figure adapted from Matthews et al. and Paul et al. [1, 2].

Figure 2: **The Construction of Organoids and Organ-on-Chips.** a) Organoids are grown by reprogramming an adult cell into a stem cell, which can specialise into different cell types under specific conditions. Stem cells are embedded into a gel that acts as a scaffold in which the stem cells divide, specialise, and grow into an organoid. b) An organ-on-a-chip containing two cell types. Two halves of a channel are prepared; one half containing a layer of one type of cell, and the other half containing another cell type. These halves are then connected with a porous membrane and the channel sealed. The resulting narrow tube has two cell types separated by a membrane, and an empty channel through which fluid can be passed.
assessed for all demographics equally. As a result, medical treatments may have different efficacies and safety profiles in women and ethnic minorities [3–11]. Using miniaturised organs derived from these underrepresented demographics could improve medical outcomes and help amend the existing biases in clinical trial populations. This approach is particularly relevant for completed clinical trials, whereas future clinical trials still require representative populations for the best medical outcomes.

Miniaturised organs also raise ethical challenges, particularly regarding the anonymisation of donations and the level of consent provided by donors [49–54]. Complete anonymisation of biological samples usually cannot be guaranteed, and re-identification may be preferred if research reveals health concerns the donor may face [49,50,54–57]. Donors should also explicitly consent to tissue collection and the specific uses of their tissue [51,53]. Additionally, donors cannot give informed consent for all future uses of donated tissue when new applications are constantly discovered. An approach of ongoing consent may therefore be suitable where donors are contacted to consent for new uses of their tissues [49,58,59].

The European General Data Protection Regulation (GDPR) was updated in 2018 with implications for research involving stem cells, including miniaturised organ research [57]. However, biological samples face unique challenges such as the inability to definitively anonymise samples. Similar ethical and regulatory issues were faced by stem cell technology and many remain unresolved, despite regulations like the GDPR. Regulations which are specific for biological applications are therefore needed [57,92].

Policy Recommendations

The implementation of miniaturised organ technology faces several challenges as outlined above. Some brief recommendations for policy development in these areas are described:

Miniaturised Organ Testing in Drug Development

Regulators should outline what they consider to be important applications of miniaturised organ testing in drug development, and how these applications could be implemented alongside animal testing. For example, drug testing could be performed on liver organoids to identify toxic by-products prior to animal testing. Regulators should provide a roadmap detailing how miniaturised organ testing might be considered in the drug approval process as the technology develops.

Miniaturised Organ Testing for Historical Clinical Trials

Many previous clinical trial populations underrepresent women and ethnic minorities [3–11]. Pharmaceutical companies should be incentivised to test medicines on miniaturised organs derived from these underrepresented groups. One solution is to implement policies that extend patent protection of a therapeutic in exchange for performing this testing.

Consent and Anonymisation in Miniaturised Organs Technology

Policies addressing the ethical concerns arising from miniaturised organ technology should be developed. Anonymisation and consent are particularly important [49,51]. Donations should require informed consent and for the donor to be aware of what degree of anonymisation is possible [54]. The donor should also agree to conditions in which they will be re-identified or contacted if new uses of their donated tissue are desired, or research using their tissue suggests a particular health risk. In the latter case the decision to contact the donor should be rapid, aligned with the
donor’s consent, and should involve the donor’s primary healthcare provider if appropriate.

Conclusion

Miniaturised organ testing has the potential to make drug development more efficient and ethical, and to partially address historical biases in clinical trials. However, proactive policies and regulations are needed to promote the beneficial uptake of this technology and to limit ethical risks. Clear regulatory guidelines are required to give businesses confidence that miniaturised organ testing will be supported in drug development. Pharmaceutical companies should also be incentivised to perform miniaturised organ testing for drugs where clinical trials have been completed but involved unrepresentative populations. Yet, these benefits of using organoids are marred by ethical challenges. Proactively addressing these issues will best allow the benefits of this technology to be realised.

© 2021 The Author(s). Published by the Cambridge University Science & Policy Exchange under the terms of the Creative Commons Attribution License http://creativecommons.org/licenses/by/4.0/, which permits unrestricted use, provided the original author and source are credited.

References


The Future of Miniaturised Organs


[16] M. Martignoni, G. M. M. Groothuis, and R. de Kanter, “Species differences between mouse, rat, dog, monkey and...


About the Author

Tim Chisholm is a 3rd year PhD student in the Department of Chemistry at the University of Cambridge, researching new amyloid-binding ligands for studying dementia. A key focus of his research is to work towards developing accurate and accessible tools for diagnosing dementia. Previously he received an undergraduate and master’s degree from the University of Sydney where he worked on improving chemical peptide synthesis using photochemistry and flow chemistry. He can be contacted at tsc42@cam.ac.uk.

Conflict of interest  The Author declares no conflict of interest.