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Organs-on-a-Chip: A Future of Rational Drug-Design

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Abstract

Many recent advances in biomedical research are related to the combination of biology and microengineering. Microfluidic devices, such as organ-on-a-chip systems, integrate with living cells to allow for the detailed *in vitro* study of human physiology and pathophysiology. With the poor translation from animal models to human models, the organ-on-a-chip technology has become a promising substitute for animal testing, and their small scale enables precise control of culture conditions and high-throughput experiments, which would not be an economically sound model on a macroscopic level. These devices are becoming more and more common in research centers, clinics, and hospitals, and are contributing to more accurate studies and therapies, making them a staple technology for future drug design.

Keywords

Organ-on-a-Chip, Microfluidics, Animal Models, Ethics, Drug Design

1. Introduction

There is a lot of debate on the actual efficacy and validity of the animal-based research. Clinicians and the public often consider it axiomatic that animal research has contributed to the treatment of human disease, yet little evidence is available to support this view [1]. The National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) performed a systematic survey of 271 animal studies and found that only 32 (12%) reported using random allocation to treatment or control and that investigators were blinded to the allocation in only 14% (5/35) of studies that used qualitative scoring [2]. Reports have also shown evidence of selective analysis, outcome reporting bias and publications bias [1] [2]. Conventional drug development comes with numerous

disadvantages; from the estimated cost of $2 million per compound tested, cultured cells not functioning as they do in the human body, the time and number of animals required for animal-based research, and the lack of translatable results produced [1] [2] [3] [4] [5]. This has led to even the most promising findings in animal research often failing in human trials and rarely being adopted into clinical practice [2].

As animal research continues to show levels of inefficiency and lack of cost-effectiveness, researchers will need to expand the range and efficacy of research options. One of the most promising research technologies, human-organs-on-a- chip, systems that could be used as specialized *in vitro* models that permit simulation, mechanistic investigation and pharmacological modulation of complex biological processes [6]. An organ-on-a-chip is a microfluidic cell culture device created with microchip manufacturing methods that contain continuously perfused chambers inhabited by living cells arranged to simulate tissue- and organ-level physiology [7]. As a replacement to animal models for drug development, organs-on-a-chip has been evaluated for many advantages and disadvantages and has shown a very wide range of applications in organ research and rational drug design.

2. Advantages Compared to Animal Based Drug Design

Traditionally, drug discovery to drug development takes place mainly in cell-culture dishes and animals, so new compounds are tested on cells that don't function like those in the human body [3] [8] [9]. This leads to 85% of therapies failing in early clinical trials, and of those that do make it to phase-III, only half are actually approved [3]-[9]. So if only 15% of the studies make it through, and even if at least a small fraction of those studies are actually approved, these models have still shown they poorly represent the complexity or nuances of human cells and systems. This leads to unreported data and wasted time and resources. Organ-on-a-chip technology is being used to develop cost-effective *in vitro* models for hit-to-lead and lead optimization that can more reliably predict the efficacy, toxicity, and pharmacokinetics of drug compounds in humans [6].

The organ-on-a-chip model approach is the development of three-dimensional cell cultures in which cells are grown within extracellular matrix (ECM) gels to induce the expression of more tissue-specific functions allows these microfluidic devices to recapitulate the physiological and mechanical microenvironment of whole living organs [10]. The example of Benam *et al.*'s study "Small airway-on-a-chip enables analysis of human lung inflammation and drug responses *in vitro*", presented the amazing potential of organ-on-a-chip technology, since the organ-on-a-chip approach represents applied synthetic biology at the organ level, it is possible to independently control and vary virtually all variables and system parameters, including the presence or absence of different cell types, vascular flow conditions and soluble factors, while simultaneously analyzing human organ-level responses in real time with molecular-scale resolution [11] [12]. Results showed, when compared to the parameters of a living human air-

way, the airway-on-a-chip mimicked structure and function characteristic in great detail [11] [12]. Huh *et al.* also provided data to show that when "mechanically active "organ-on-a-chip" micro devices that reconstitute tissue-tissue interfaces critical to organ function may, therefore, expand the capabilities of cell culture models and provide low-cost alternatives to animal and clinical studies for drug screening and toxicology applications" [13] [14] [15].

Various studies have found significant success utilizing the lung-on-a-chip model. Jain *et al.* utilizing the chip model to examine intravascular thrombosis for assessment of therapeutics had demonstrated that the primary-human-lung-alveolus-chip permits the visualization and quantitative real-time analysis of organ-level interactions relevant to in situ thrombus formation in the human lung. The lung-on-a-chip model allowed Jain *et al.* to dissect contributions of various human cell types and tissues [16] [17]. The lung-on-chip model successfully integrated epithelial and endothelial cells on either side of a membrane, within a device also mimicking the mechanical stress due to respiration has allowed for the examination of proinflammatory signals, such as TNF-α and LPS, and fluid flow, as well as the contribution of potential antithrombotic and anti-inflammatory therapeutics, which would be nearly impossible to perform *in vivo* [11] [12] [16] [17].

3. Disadvantages Compared to Animal Based Drug Design

Even with the extensive possibilities that organs-on-a-chip are capable of, reaching the full capabilities of these new devices requires more work. One of the biggest technical challenges with the current organ-on-a-chip designs stems from materials. One example would be poly (dimethylsiloxane) (PDMS) which has been shown to absorb small hydrophobic molecules, which can negatively affect drug concentrations and pharmacological activities [3] [6] [7]. Another major issue that organ-on-a-chip technology faces are finding the balance between complexity and practicality, with increasing complexity improves the organ-on-a-chip's physiological relevance but lowers the practicality of control and management of the system in question [3].

The organ-on-a-chip must deal with dynamic technical challenges, such as bubbles in microfluidic channels which can cause damage to the cells and hamper chip controls, consistent cell seeding in microfluidic channels, preventing microbial contamination, and controlling proper cell-to-cell interactions [7]. Organ-on-a-chip models are still far from recreating the complex biology of the endocrine, immune and nervous systems, which animal models are still better suited for [6].

Low and Tangle had found challenges in "cell sourcing, as primary cells from human tissue can be difficult to obtain" as well as difficulty utilizing induced pluripotent stem cells (iPSCs) since "some organ tissues are less amenable to differentiating into the tissues of choice, and the lack of standardized protocols can lead to large heterogeneity in phenotype and maturity of cells" [8] [18].

4. Current and Future Applications in Research and Drug Design

Researchers have created organs-on-a-chip for the study of the liver, kidney, intestine, lung, heart, smooth and striated muscle, fat, bone, marrow, cornea, skin, blood vessels, nerve and blood-brain barrier, among other organs [7]. The constant expansion of distinct organ-on-a-chip models provide opportunities to explore many organs that have yet to be explored in their desired field. Organ-on-a-chip technology can be synergistically integrated with modeling and analysis tools already used in drug discovery. Organs-on-chips also have advantages over current animal models. Animal studies can effectively emulate the physiological complexity at the whole-organism level, animal model based carriers of human diseases are now facing increased scrutiny and skepticism regarding their scientific validity and translatability to humans in clinical evaluations [6].

With conventional cell culture methods, it has proven to be difficult to mimic *in vivo*-like microenvironments as well as difficulty to provide a number of well-controlled stimuli that are critical for stem cell culture and differentiation. The utility of organs-on-a-chip to model 3D organ biology can allow for new ways to study stem cell differentiation and maturation in *in vivo*-like systems, and help advance the potential of stem cell therapies and regenerative medicine [18] [19]. Microfluidic devices, which can control multiple soluble and physical factors simultaneously with high precision, provide an ideal and well-defined platform for stem cells, helping with studies such as gene transfection, the study of the genetic states of stem cells, as well as the development of a wide variety of microplatforms. Zhang *et al.* present that various types of stem cells such as ESCs, neural stem cells, induced PSCs, HSCs and MSCs derived from different tissue sources were integrated in different microfluidic systems and through ability of microfluidics to control stem cell microenvironments with high spatial and temporal precision and the ability to conduct experiments under conditions resembling *in-vivo* environments and situations through properly designed microstructures, surface modification and integration of biocompatible extracellular materials, it is feasible to maintain a suitable microenvironment for stem cell natural growth. [18] [19] [20].

The envisioned commercially relevant applications for organ-on-a-chip models are multi- and singular organ models for drug toxicity screening, human disease models for drug target discovery and drug development, and models to investigate routes for drug uptake, such as drug metabolism in the gastrointestinal system or uptake via inhalation in the lungs [21]. Other possibilities for future studies include the development of predictive human disease models. One area of interest is to use organs-on-a-chip to model pediatric diseases and rare diseases, studies of which are limited due to the lack of in vitro modeling approaches, small patient populations and limited patient availability [6]. One application which would be critical to the future of the organ-on-a-chip model would be the design and application of a human-body-on-a-chip. The chip

model built to simulate the physiology and pathology of the human body, which with such a large range of application, could bridge the gap between clinical and animal testing, possibly even eliminating the necessity of animal testing as a whole [13] [14] [15] [18] [22]. With conventional cell culture methods, however, it has proven to be difficult to mimic *in vivo* like microenvironments.

5. Conclusion

With the value of animal research being called into question, and as more meta- and systematic research questioning this value continues to become more prevalent, alternative solutions will continue to become more desirable. The organ-on-a-chip technology has shown a possibility to be more efficient for research time and finances, as well as having a greater level of translation from *in vitro* research to clinical research. Current models, such as the lung-on-a-chip, have demonstrated that this design can mimic the innate cellular responses to pulmonary infections, as well as the anatomical and physiological complexity of the human organ [6] [13] [14] [15]. Lin *et al.* presented the possibilities of a new multi-layer microfluidic device for effective assessment of drug metabolism, drug efficacy and toxicity in different organ-specific cells simultaneously when measured next to *in vivo* models [22]. With the possibility to replicate the human organ's physiology and potentially the human body as a whole, the organ-on-a-chip model can become a primary model for the study of toxicity and the pharmacokinetics and the pharmacodynamics of drug compounds.

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References

[1] Pound, P., Ebrahim, S., Sandercock, P., Bracken, M.B. and Roberts, I. (2004) Reviewing Animal Trials Systematically (RATS) Group. Where Is the Evidence That Animal Research Benefits Humans? *BMJ*: *British Medical Journal*, **328**, 514-517. https://doi.org/10.1136/bmj.328.7438.514

[2] Pound, P. and Bracken, M.B. (2014) Is Animal Research Sufficiently Evidence Based to Be a Cornerstone of Biomedical Research? *BMJ*, **348**, g3387. https://doi.org/10.1136/bmj.g3387

[3] Larkin, M. (2015) Could Organs-On-Chips Replace Drug Testing on Animals? https://www.elsevier.com/connect/could-organs-on-chips-replace-drug-testing-on-animals

[4] Perel, P., Roberts, I., Sena, E., Wheble, P., Briscoe, C., Sandercock, P., *et al.* (2007) Comparison of Treatment Effects between Animal Experiments and Clinical Trials: Systematic Review. *BMJ*, **334**, 197. https://doi.org/10.1136/bmj.39048.407928.BE

[5] Joffe, A.R., Bara, M., Anton, N. and Nobis, N. (2016) The Ethics of Animal Research: A Survey of the Public and Scientists in North America. *BMC Medical Eth-*

ics, **17**, 17. https://doi.org/10.1186/s12910-016-0100-x

[6] Esch, E.W., Bahinski, A. and Huh, D. (2015) Organs-On-Chips at the Frontiers of Drug Discovery. *Nature Reviews Drug Discovery*, **14**, 248-260. https://doi.org/10.1038/nrd4539

[7] Bhatia, S.N. and Ingber, D.E. (2014) Microfluidic Organs-On-Chips. *Nature Biotechnology*, **32**, 760-772. https://doi.org/10.1038/nbt.2989

[8] Ingber, D.E. (2016) Reverse Engineering Human Pathophysiology with Organs-On-Chips. *Cell*, **164**, 1105-1109. https://doi.org/10.1016/j.cell.2016.02.049

[9] Ledford, H. (2011) Translational Research: 4 Ways to Fix the Clinical Trial. *Nature*, **477**, 526-528. https://doi.org/10.1038/477526a

[10] Huh, D., Leslie, D.C., Matthews, B.D., Fraser, J.P., Jurek, S., Hamilton, G.A. and Ingber, D.E. (2012) A Human Disease Model of Drug Toxicity-Induced Pulmonary Edema in a Lung-on-a-Chip Microdevice. *Science Translational Medicine*, **4**, 159ra147. https://doi.org/10.1126/scitranslmed.3004249

[11] Benam, K.H., Villenave, R., Lucchesi, C., Varone, A., Hubeau, C., Lee, H., Ingber, D.E., *et al.* (2015) Small Airway-on-a-Chip Enables Analysis of Human Lung Inflammation and Drug Responses *in Vitro*. *Nature Methods*, **13**, 151-157. https://doi.org/10.1038/nmeth.3697

[12] Truskey, G. (n.d.) Faculty of 1000 Evaluation for Small Airway-on-a-Chip Enables Analysis of Human Lung Inflammation and Drug Responses *in Vitro*. F1000 Post-Publication Peer Review of the Biomedical Literature.

[13] Huh, D., Matthews, B.D., Mammoto, A., Montoya-Zavala, M., Hsin, H.Y. and Ingber, D.E. (2010) Reconstituting Organ-Level Lung Functions on a Chip. *Science*, **328**, 1662-1668. https://doi.org/10.1126/science.1188302

[14] Zimmerman, G. (n.d.) Faculty of 1000 Evaluation for Reconstituting Organ-Level Lung Functions on a Chip. F1000 Post-Publication Peer Review of the Biomedical Literature.

[15] Laffey, J. (n.d.) Faculty of 1000 Evaluation for Reconstituting Organ-Level Lung Functions on a Chip. F1000 Post-Publication Peer Review of the Biomedical Literature.

[16] Jain, A., Barrile, R., Meer, A.V., Mammoto, A., Mammoto, T., Ceunynck, K.D. and Ingber, D. (2017) Primary Human Lung Alveolus-on-a-Chip Model of Intravascular Thrombosis for Assessment of Therapeutics. *Clinical Pharmacology & Therapeutics*. https://doi.org/10.1002/cpt.742

[17] Luni, C., Serena, E. and Elvassore, N. (2014) Human-on-Chip for Therapy Development and Fundamental Science. *Current Opinion in Biotechnology*, **25**, 45-50.

[18] Low, L. and Tagle, D. (2017) Microphysiological Systems ("Organs-on-Chips") for Drug Efficacy and Toxicity Testing. *Clinical and Translational Science*, **10**, 237-239. https://doi.org/10.1111/cts.12444

[19] Zhang, J., Wei, X., Zeng, R., Xu, F. and Li, X. (2017) Stem Cell Culture and Differentiation in Microfluidic Devices toward Organ-on-a-Chip. *Future Science OA*, **3**. https://doi.org/10.4155/fsoa-2016-0091

[20] Park, D., Lim, J., Park, J.Y. and Lee, S. (2015) Concise Review: Stem Cell Microenvironment on a Chip: Current Technologies for Tissue Engineering and Stem Cell Biology. *STEM CELLS Translational Medicine*, **4**, 1352-1368. https://doi.org/10.5966/sctm.2015-0095

[21] Van de Stolpe, A. and Toonder, J. (2013) Workshop Meeting Report Organs-on-Chips: Human Disease Models. Lab on a Chip, 13.

https://doi.org/10.1039/c3lc50248a

[22] Li, Z., Guo, Y., Yu, Y., Xu, C., Xu, H. and Qin, J. (2016) Assessment of Metabolism-Dependent Drug Efficacy and Toxicity on a Multilayer Organs-on-a-Chip. *Integrative Biology*, **8**, 1022-1029. https://doi.org/10.1039/C6IB00162A