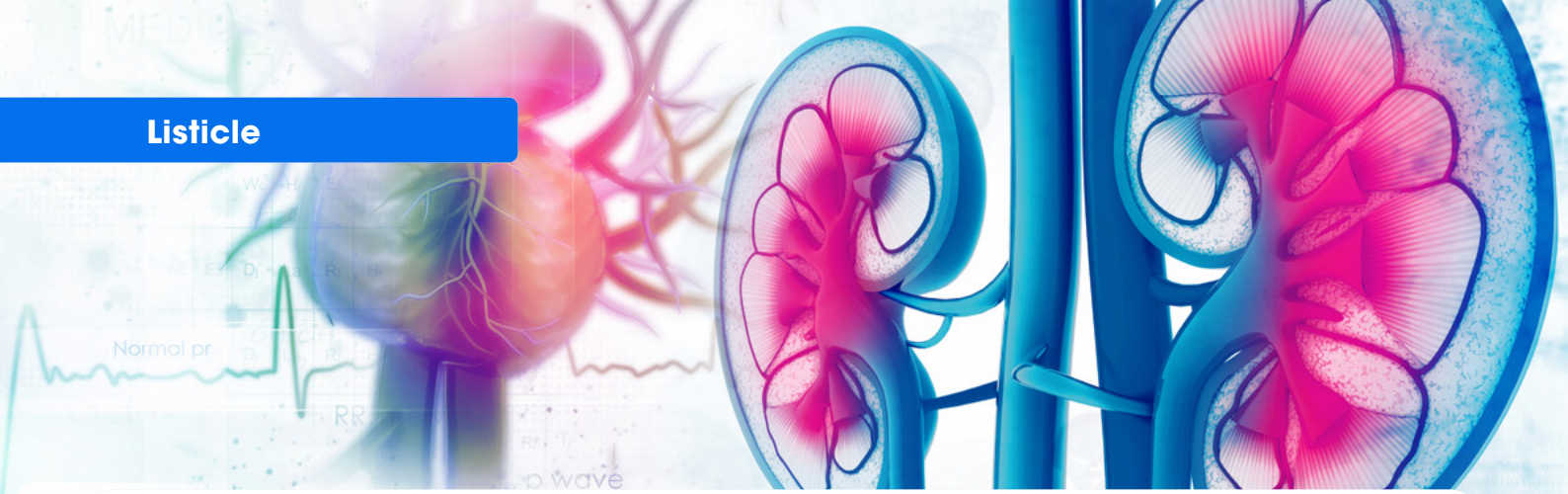
Listicle



5 Unique Ways Organ-on-a-Chip Technology Is Being Applied in Biomedical R&D

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Organ-on-a-chip (OOAC) technology is a promising tool with numerous applications across biomedical fields. Also known as microphysiological systems, tissue chips or organs-on-chips, these devices offer a way to replicate key aspects of human physiology, and therefore answer specific questions about organ function and disease pathophysiology.[1] OOAC technology also presents new opportunities for evaluating drug pharmacokinetics and pharmacodynamics, including the efficacy of a drug, drug–drug interactions and potential toxicity.

The development of OOAC technology is challenging, requiring the convergence of engineering and biological expertise, with many complex microphysiological system components. Devices can be developed to mimic aspects of either single or multiple organs, with the latter referred to as body-on-a-chip or human-on-chip systems.[2] OOAC technology has been described as "ambitious", and there are many challenges; devices need to be simple enough to build, but without oversimplifying to the extent that physiological relevance is lost.[3] OOAC systems must host a viable cell culture long enough to facilitate the desired studies, and there are many functional parameters to build in, such as perfusion, waste removal, mechanical stimulation (e.g., shear stresses and stretching), and physicochemical parameters such as temperature, pH, oxygen and CO_2.[3]

Despite the many challenges, OOAC technology is seen as a highly beneficial pursuit, given their ability to provide insights that cannot be obtained using standard cell culture models.[4] It has been predicted that the uptake of OOAC systems could improve the success rates of drug development, thereby reducing R&D costs by 10–26%.[5] Such savings are bound to benefit patients, and are in line with principles of the 3Rs in animal research. To provide an insight into the applications of OOAC platforms, this listicle explores five recent publications involving OOAC systems.

1. Blood vessel-on-chip used to inspect rejected therapeutic for autoimmune disorders

An OOAC device designed to model human blood vessels was used to provide a deeper understanding of serious adverse effects observed in clinical studies.[6] A monoclonal antibody (mAb), Hu5c8, was intended for the treatment of autoimmune disorders. After sailing through preclinical testing, Hu5c8 was put forward for clinical trials. While its intended mechanism – blocking of a key step in the initiation of the adaptive immune response (T-cell activation via binding of the CD40 ligand to its receptor) – is a validated

therapeutic strategy, development of these targeted mAbs was halted when thrombosis and cardiovascular events were observed during clinical trials.

To explore the mechanisms associated with these events, an OOAC model was developed, comprising a layer of human endothelial cells which were perfused with whole blood. The ability to analyze a number of physiologically relevant endpoints was also built in, like platelet aggregation and fibrin clot formation. The developed OOAC platform was found to be a useful platform for studying and predicting the risk of thrombotic side effects of drug candidates.

After model validation, a few novel findings were observed which helped to shed light on the potential mechanisms of thrombosis induced by Hu5c8, and possible risk factors which can be studied in the future. Thrombosis induced by Hu5c8 is thought to be dependent on a particular receptor (FcγRIIa), and further support for this hypothesis was found using the OOAC model; an antibody formatted to not bind to the FcγRIIa receptor did not induce fibrin clot formation (an indication of thrombosis potential). It is hoped that this OOAC platform could be used to assess the new generation of mAbs directed at the CD40 pathway and provide a means of risk assessment for a broad class of molecules.

2. An OOAC platform for liver disease modeling and drug screening

Many OOAC platforms have been used to model a range of diseases, including nonalcoholic fatty liver disease (NAFLD). NAFLD is a spectrum of diseases resulting from fat accumulation in the liver, through to the potentially cirrhosis- and cancer-inducing condition of nonalcoholic steatohepatitis (NASH). To better understand the trajectory of this disease pathway, researchers sought to develop *in vitro* models of liver disease using OOAC technology.

Kostrzewski et al. (2020) developed a co-culture OOAC model that mimics features of NASH.[7] The perfused model is composed of three cell types: primary human hepatocytes, human Kupffer cells and hepatic stellate cells, and can be maintained for at least two weeks to allow different stages of disease progression to be studied. The NASH model was further characterized and extended in a 2021 study when Kostrzewski et al. (2021) exposed the co-culture to different cues and measured the effect on markers of different stages of pathogenesis.[8] For example, inflammation and fibrosis in NASH was driven by exposure to a combination of FFA, TGFβ and fructose, while earlier stages of NASH were observed after FFA alone or in combination. Here, the ability to measure fat accumulation, pro-inflammatory cytokine production and hallmarks of fibrosis are all important to using the model for drug discovery. This level of characterization was achieved with the use of RNAseq, multiplexed assays and a quantitative, automated imaging assay for fibrosis – techniques which will allow a wide range of fundamental and drug development studies to be completed in the future.

3. On-chip model for therapeutics targeted at preventing acute kidney injury

Vormann et al. (2022) describe the development of an OOAC platform which shows promise as a robust model for acute kidney injury and high-throughput drug testing.[9] Specifically, the model was aimed at capturing key features of renal ischemia/reperfusion injury (rIRI), one of the most common causes of acute kidney injury. rIRI may occur after patients experienced a disruption to their renal flow, such as through heart failure, hemorrhage, cancer or a blood clot. The resulting damage to the proximal tubule structure is particularly topical at present, as it is a symptom experienced by some with severe SARS-CoV-2 infection.

rRIRI was mimicked on a renal proximal tubule-on-a-chip, co-cultured with endothelial cells. The OOAC model allowed many adjustments to culture settings, to enable studies of ischemic conditions and their role in inducing kidney injury. Adjustments to nutrient composition, oxygen tension and perfusion flow were made, followed by morphological assessment and measures of cell viability and caspase-3/7 activation (indicators relevant to apoptotic activity). Furthermore, the renoprotective effects of adenosine were characterized, highlighting the potential of this kidney-on-a-chip model for supporting the development of therapeutics aimed at preventing acute kidney injury.

4. An airway-on-a-chip for discovering antiviral therapeutics and prophylactics

The development of OOAC technology is aimed partly at accelerating the identification of therapeutics, and infectious disease is no exception. A bronchial-airway-on-a-chip was shown to be a suitable tool for modeling the response of human lung tissue to viral infection.[10] The chips are comprised of cultured primary human lung bronchial-airway basal stem cells on one side of a membrane, interfaced with human lung endothelium on the other side. The stem cells differentiate into a mucocilated epithelium with a range of cell types similar to those found *in vivo*, including ciliated cells, mucus-producing goblet cells, club cells and basal cells.

Si et al. (2021) demonstrated the use of this airway-on-a-chip platform for modeling viral infection, strain-dependent virulence, cytokine production and immune cell recruitment. This was achieved by comparing responses to infection with three patient-derived influenza A strains with differing virulence; here, higher concentrations of cytokines and chemokines were measured in chips infected with viruses known to produce more severe clinical symptoms. To test the ability of the chip to reflect changes induced by known therapeutics, an active metabolite of Tamiflu (the most widely used anti-influenza drug) was introduced to the chip. Here, a number of effects typically observed *in vivo* were reflected in the chip; specifically, the inhibition of influenza A virus replication, reduction of cytokine and chemokine production, prevention of epithelial tight junction disruption, and prevention of virus-induced compromise of barrier function. Together, the findings support the future use of this airway-on-a-chip for future preclinical evaluations of therapies against lung infection.

5. A liver-on-a-chip tool for assaying drug toxicity, metabolism and accumulation

While there have been significant advances in OOAC platform development (probably more than it seems, as pointed out in this article), quality control metrics are needed to help implement OOAC technology on a routine basis. The reproducibility of a liver-on-a-chip platform was therefore assessed in a publication uniquely co-authored by both FDA scientists and the on-chip developer.[11] Experiments assaying drug toxicity, metabolism and intracellular accumulation were compared across two test sites with different batches of cells cultured in the chips. The study is an important step forward for helping to bring OOAC technology a step closer to routine use in drug development, and results were positive; the liver-on-a-chip platform reproducibly detected drug toxicity induced by a range of drugs, enabled studies of hepatic function, and provided metabolic information that could support the interpretation of clinical data.

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