Bench to Bedside

Body-on-a-Chip Reveals Multitissue Interactions During Drug Exposure

Tracy Hampton, PhD

By generating bioengineered organoids of the liver, heart, and lungs and connecting them in a closed system with a nutrient-rich liquid to mimic the body's circulatory system, researchers have created a "body-on-a-chip" that may help reveal interorgan responses to drug or toxic chemical exposure. The potential to do so has implications for drug development, considering that many drugs have progressed through years of preclinical studies, clinical trials, and market availability before being recalled.

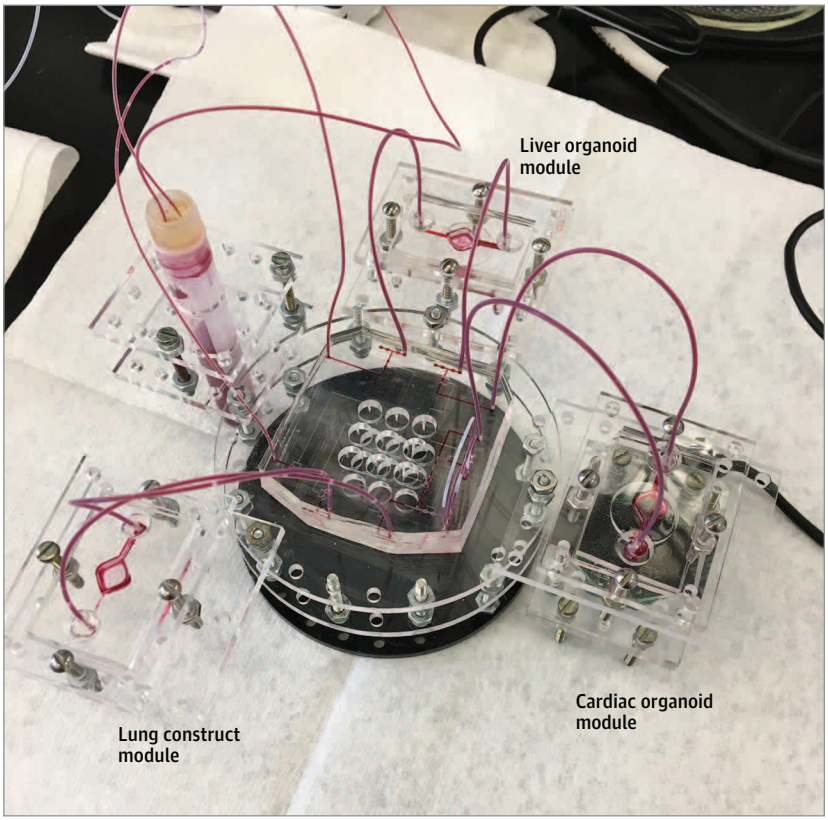
As detailed in their *Scientific Reports* study, each organ model was created with the cell types present in native human tissue. Bioprinting technologies were used to integrate liver and cardiac organoids into modular perfusable devices connected to a lung organoid at the air-liquid interface. Liver and heart toxicity account for the majority of drug candidate failures and recalls, and the lung serves as a unique point of entry for aerosolized toxic particles.

"How an individual organ responds to a drug is important, but more important is how the whole body responds," said Anthony Atala, MD, director of the Wake Forest Institute for Regenerative Medicine and senior researcher on the project. "There are many examples of drugs approved for use in patients that have to be taken off the market due to unexpected toxic effects in tissues and organs not directly targeted by the medications."

Because organs in the body do not exist in isolation and are functionally interconnected, Atala and his colleagues developed their system to better emulate their interactive nature. "We are of course not the only group working in this field of organoids and organ-on-a-chip systems. Right now we're seeing a tremendous amount of work in many laboratories across the country and world," said Aleksander Skardal, PhD, assistant professor at the Wake Forest Institute for Regenerative Medicine and first author of the article. The National Institutes of Health recently announced 13 new awards to develop tissue-chip models of disease. "However, only a few examples have been demonstrated in which multiple highly functional bioengineered 3D [3-dimentional] organs, or organoids, are combined within a single system and are successfully maintained for any extended period of time," said Skardal.

Robert Lanza, MD, chief scientific officer at Astellas Institute for Regenerative Medicine, who was not involved in the study, noted that although new advancements have allowed for the development of numerous 3D organ models, "this is by far the most advanced system reported to date.... and more closely reflects the complex physiological interactions that occur naturally in the human body." According to Gordana Vunjak-Novakovic, PhD, director of the Laboratory for Stem Cells and Tissue Engineering at Columbia University, the system also addresses an important unsolved problem in that it "provides connections between different tissue organoids by circulatory perfusion."

The study describes the system and the experiments validating its potential utility. For example, because the liver metabolizes propranolol, rendering it ineffective at blocking cardiac β-receptors, the



Researchers bioengineer organoids of the liver, heart, and lungs and connect them in a closed system to create a "body-on-a chip." The system may aid drug development by revealing interorgan responses to drug exposure.

Aleksander Skardal, PhD/Wake Forest Institute for Regenerative Medicine

researchers examined the effects of propranolol with and without liver organoids. In the system without liver organoids, propranolol remained in its active form and successfully blocked epinephrine from binding cardiac β-receptors and increasing the rate of cardiac beating; however, when 3D liver organoids were introduced, they metabolized the propranolol and beating rates increased after administration of epinephrine. Propranolol did not have these same effects when applied to a dual-component liver-heart system containing 2D hepatocyte cultures, suggesting 2D cultures do not model organ metabolism as well as 3D organoids.

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The researchers also found that when the cancer drug bleomycin, which adversely affects the lungs, was introduced into the 3-organoid system, scarring of the lungs occurred as expected, but in addition, the heart organoid stopped beating. Subsequent experiments indicated that the effect may be due to inflammatory proteins from the lungs circulating throughout the system. "This is an example of an unanticipated side effect in an off-target tissue, which is the exact type of result that these multitissue platforms enable during drug development," said Skardal.

The investigators were surprised to find that they did not need complicated tissue culture media to support the different cell types. "Traditionally, in 2D tissue culture, maintaining cells—like primary human hepatocytes, stem cell–derived cardiomyocytes, and others—can be difficult. They all require very specific and expensive media formulations," said Skardal. "As we began working to integrate multiple tissue organoid types, what we thought would be perhaps the most difficult hurdle of the project was actually much simpler in practice. These 3D organoids, when integrated, are much more robust than we expected."

As noted in the study, the screening and the development processes for safe and effective medications can exceed $2 billion in the United States each year, and more than 90% of drugs that enter phase I clinical trials ultimately fail. This model system may provide valuable information that will improve and speed up these processes so that safe and effective drugs reach patients sooner and at a lower cost, the authors explain.

Organ-on-a-chip systems are not yet at a stage where they can be easily deployed in high-throughput screening, and it will be important to integrate other organs beyond the heart, liver, and lungs. Nevertheless, Vunjak-Novakovic stressed that some of the most advanced multitissue platforms are already being used by pharmaceutical companies for drug development and testing.

Considering organoids can be generated from patient-derived cells, the research might also be used in personalized medicine to help predict an individual patient's response to a particular treatment, noted Atala. ■

Note: Source references are available through embedded hyperlinks in the article text online.