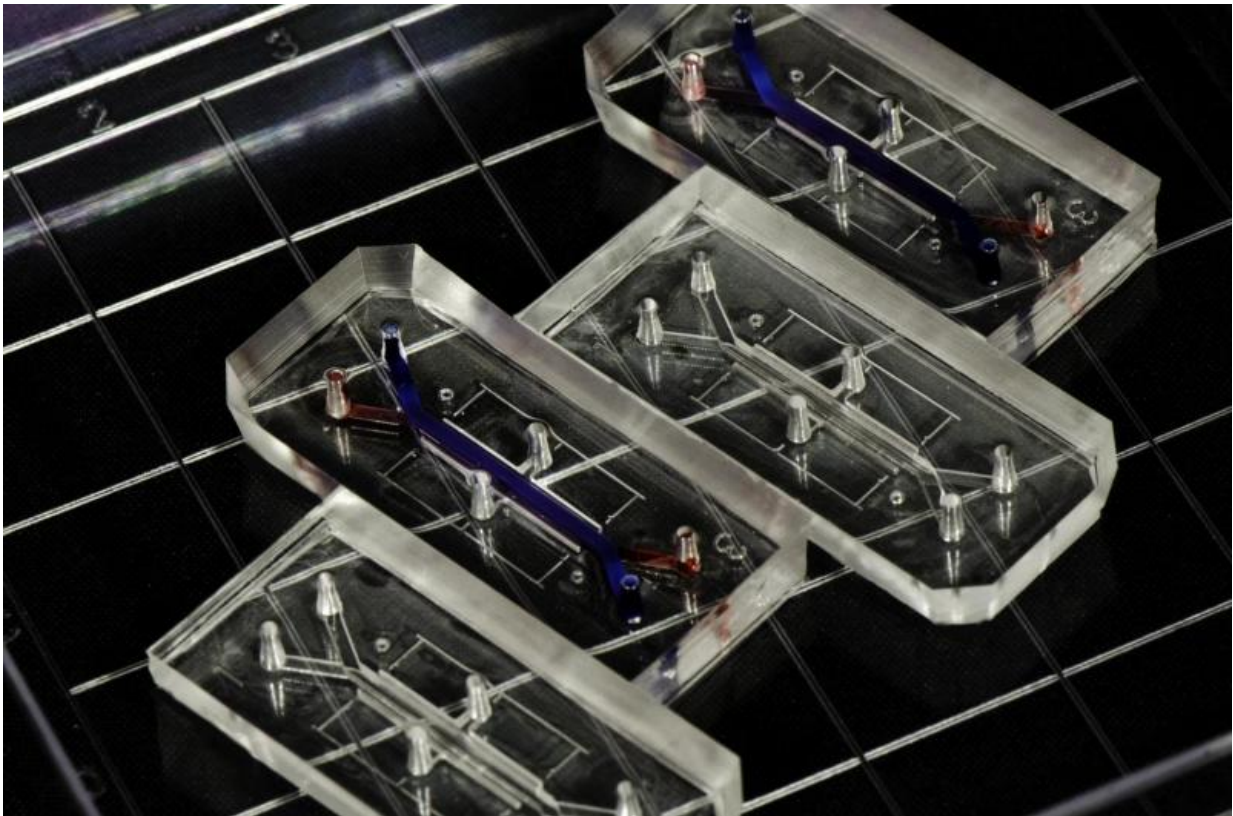


# Reverse engineering human biology with organs-on-chips

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Organs-on-chips, crystal clear, flexible polymers about the size of a computer memory stick that contain hollow channels fabricated using computer microchip manufacturing techniques. These channels are lined by living cells and tissues that mimic organ-level physiology. Credit: Wyss Institute at Harvard University

"Organs-on-Chips," added last May to the collection of the Museum of

Modern Art in New York City and winner of the 2015 Design Award from the London Design Museum, have kept their "classical" design over the years, but have grown in complexity thanks to recent advances. The family of chips, which are microfluidic devices containing hollow channels lined by living human cells, now includes everything from a lung-on-a-chip to an intestine-on-a-chip to a blood-brain-barrier-on-a-chip. Each device essentially reconstitutes a functional interface between two living human tissues, with one being lined by blood vessel cells containing flowing fluids with life-sustaining nutrients, while the whole device mimics the physical environment (breathing motions in the lung, peristalsis in the gut) of living organs within the human body.

While some suggest that the devices oversimplify human biology, by reverse engineering organ structure, the chips have been able to reconstitute complex organ-level functions, which has led to new insights into what is and what isn't necessary for life to function. In a Commentary, published March 10 in *Cell*—part of a special issue on the biology of communication—Donald Ingber, director of the Wyss Institute for Biologically Inspired Engineering at Harvard University, describes how organs-on-chips offer a powerful new way to analyze organ function and human pathophysiology, in addition to providing a potential way to replace animal testing and advance personalized medicine.

"We're not trying to rebuild a [human organ](#)," Ingber says. "We're trying to develop culture environments for living [human cells](#) with the minimal design features that will induce them to reconstitute organ level structures and functions to mimic the physiology that we see in the [human body](#)."

Ingber sees modeling a human organ as a systems-level challenge. While recent advances in organoids provide new opportunities to observe and manipulate human tissue development in vitro, researchers can use

organs-on-chips to study how multiple different types of [cells](#) and tissues—including epithelium, vascular endothelium, [immune cells](#), and both commensal and pathogenic microbes—communicate to regulate pathophysiology in whole organisms. "Communication in biology is information transfer," he says. "Whether that's at the molecular, cellular, tissue, organ, or the whole-body level, what makes life is that that information is integrated across multiple size scales and across multiple levels of complexity."

For example, the lung-on-a-chip, developed by Ingber in 2010 with biomedical engineer Dongeun (Dan) Huh, started with the bare minimum of two closely juxtaposed tissues—one a layer of lung air sac cells and the other [blood vessel cells](#)—in a two-channel device in which the lung cells are covered by air, and fluid medium containing human [white blood cells](#) is continuously flowed over the vessel cells much like blood flows through the vessels of our bodies. The chip also exposes the tissues to cyclic stretching and relaxation movements that mimic breathing motions. With the chips, researchers can measure how bacterial infections or airborne particulates induce injury and inflammation, as well as how certain drugs induce fluid shifts into the air space that cause pulmonary edema. More recently, lung small airway chips created with [lung cells](#) taken from patients with chronic obstructive pulmonary disease (COPD) were shown to mimic exacerbations of lung inflammation induced by viral or bacterial infections similar to those seen in COPD patients.

Despite being an abstraction of the lung, the biology seen on the chip consistently reproduces responses observed in animals as well as in humans. Different organ chips also have been linked by flowing medium to model how multiple organs interact. Some of the most surprising findings from these experiments relate to how little you need to replicate what is often considered complex biology.

"With organs-on-chips, we can have a combination of two or three tissue types then add, immune cells or microbes," Ingber says. "We can then selectively modify each control parameter and see what it does—how each contributes alone, how do they contribute together, or in different combinations—I don't know of any other system where we can do that with human cells at the tissue to organ level."

The combination of organ-on-chips with stem cell technology also offers possibilities for enhancing personalized medicine. For example, Ingber suggests that by generating induced pluripotent stem cell-derived human tissue from patients, it could be possible to screen for drugs on chips created with their cells, and then, if successful, test the potential drug on the same patients. This type of personalized drug development program would save money in failed clinical trials and hasten the ability of new drugs to reach patients who would immediately benefit.

"Organs-on-chips allow one to do research that is immediately much more relevant to humans than working with animal cells or even [human cells on rigid dishes](#)" Ingber says. "I think the idea of personalized medicine, combining chips with induced [pluripotent stem cells](#), could be transformative."

**More information:** *Cell*, Ingber: "Reverse Engineering Human Pathophysiology with Organs-on-Chips"  
[dx.doi.org/10.1016/j.cell.2016.02.049](https://doi.org/10.1016/j.cell.2016.02.049)

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