

# Horizons in Bioscience

## ORGANS-ON-A-CHIP

### The Future of Drug Development and Study of Disease

Imagine if, before you ever took a drug, doctors could predict which drug would work best for *you*, because they already had information on how organs in *your* body were likely to respond. Organs-on-a-chip research is bringing that day closer. This emerging technology allows scientists to watch the cascade of events that takes place in organs in response to drugs or during disease.

**ORGANS-ON-CHIPS** are 3-D biochips, no bigger than a computer memory stick, that contain living human cells from an organ or tissue. Engineered in layers and channels, substances such as air or blood can be delivered continuously, and the cells can interface with other living tissues as they do in the body. Mechanical forces replicate breathing, blood flow, or muscle contractions.

in the body. Scientists can even include multiple cell types in the channel to more accurately mimic complex structures in the living organ. Second, add fillings involved in that organ's function, such as nutrients and oxygen. Finally, add mechanical forces (e.g., breathing or the motion of the gut) in the same proportions as those occurring in the actual organ.

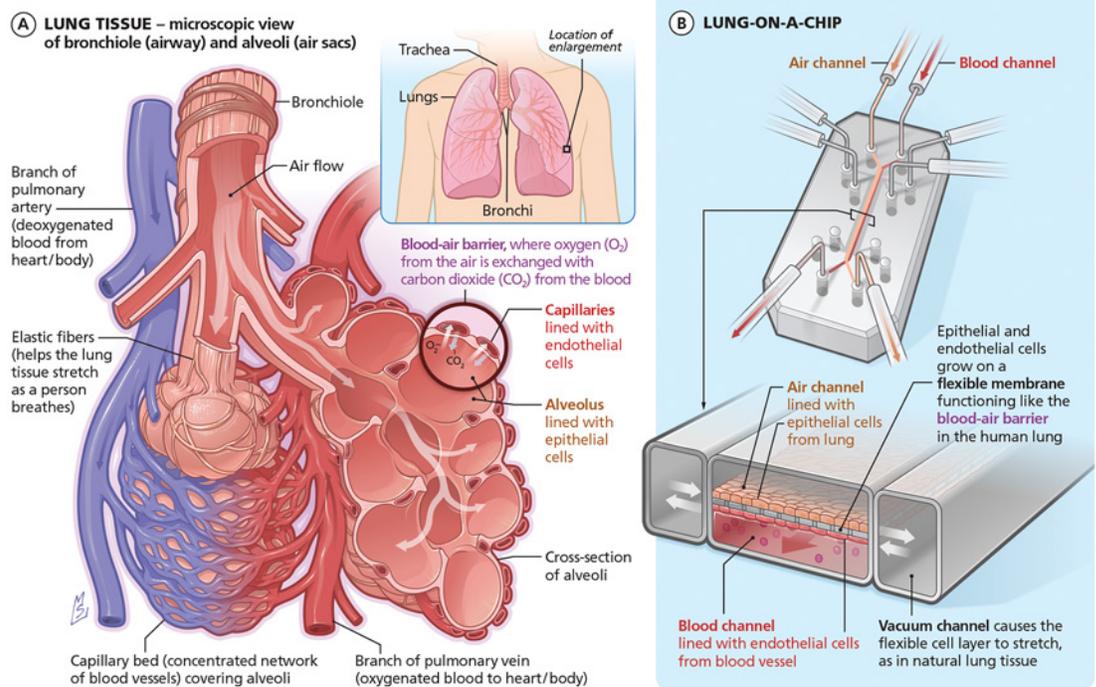
### Organs-on-chips at work

One impetus for the new technology is to improve drug testing. On average, it takes 12 years and billions of dollars for new drugs to reach the market. Most never make it that far. Many are eliminated when animal testing uncovers toxicity or other problems. Others are discarded when testing in humans shows they aren't as safe or as effective as predicted.

### Engineering organs-on-chips

Cells grown in petri dishes receive nutrients, but they are isolated from the cell's normal environment in the body. When scientists grow cells in 3-D chips, they can add cellular interactions and mechanical forces so that the cells feel—and act—right at home.

Making organs-on-chips is like preparing a layer cake. Using microengineering techniques, scientists begin by building a plastic mold with hollow channels. Once the mold hardens into a flexible, transparent chip, it's time to add the ingredients. First, line the channels with living human cells. The cells can be taken directly from the desired organ or lined with stem cells, which can mature into any type of cell



**Lung-on-a-chip:** In a human lung (A), oxygen from the air is inhaled and travels to the lung's air sacs (alveoli). There, the oxygen is exchanged with carbon dioxide from the blood (blood-air barrier), and the carbon dioxide is exhaled. The lung-on-a-chip (B) mimics the human lung. Blood vessel cells (endothelial) and lung cells (epithelial) line opposite sides of a porous membrane. Air and blood are flowed over the cell-covered membrane, and oxygen and carbon dioxide are exchanged at the blood-air barrier. A vacuum simulates inhalation and exhalation. *Illustration: © Michael Linkinhoker, Link Studio, LLC.*

Organs-on-chips have the potential to shorten the time and cost of new drug development by identifying these problems early. Because organs-on-chips can be made with cells representing different populations, they can address differences between groups. Men aren't the same as women. Children are not the same as adults, nor do different populations always respond to drugs identically. Furthermore, it is difficult to study rare diseases, problematic to conduct studies in pregnant women or infants, and unethical to expose people to lethal toxins. Thus, organs-on-chips enable researchers to study things that would not be possible otherwise.

### Some current applications of organs-on-chips:

**Lung:** The interface of lung and capillary cells is where many health problems begin, such as inflammatory responses to environmental toxins. It's also where aerosol-based drugs enter the body. The Wyss *Lung-on-Chip* recently was used to model inflammation and to create fluid on the lungs (pulmonary edema). This life-threatening condition can occur as a side effect of a chemotherapy drug. By watching the *Lung-on-Chip* react to this drug, the team saw that breathing motions worsened the drug's toxicity. The surprising finding could lead to new ways to minimize this side effect.

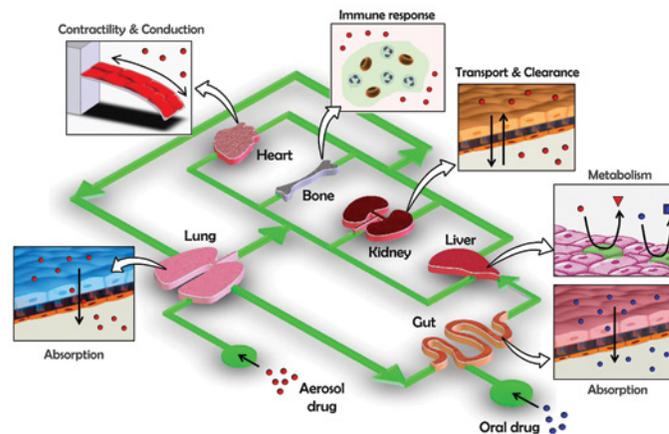
**Artery:** Organ-chips are not only about acute disease. The *artery-on-a-chip* developed at the University of California Davis gives researchers an unprecedented view of how atherosclerosis develops in coronary arteries and how activation of white blood cells related to inflammation (monocytes) influences the risk of heart problems. This improved understanding could lead to novel anti-inflammation therapies and, eventually, to new tools to predict, monitor, and treat atherosclerosis. Other hearts-on-chips are studying whether new drugs have heart-damaging side effects.

**Gut:** In the Wyss *Gut-on-Chip*, a thin membrane is lined by intestinal cells, and the microenvironment of the intestine is recreated by flowing liquid through adjacent channels and exerting pressures similar to the motion of the gut. Under these conditions, the cells spontaneously develop the hair-like projections (villi) that cover the lining of the small intestine. Researchers have even been able to grow microbes on the surface of intestinal cells in the chip, an important step forward in culturing more of the living bacteria from the gut. Although work remains in recreating all aspects of the human intestine, the *Gut-on-Chip* could become an essential tool in examining how drugs are absorbed through the intestine and in studying digestive diseases.

Other organs-on-chips in development include bone and cartilage, bone marrow (important in studies of radiation), brain (important in studies of drug permeability), cornea, fat, kidney, liver (the major organ of drug metabolism), nerves, pancreas (essential in studies on insulin-producing cells), reproductive tract, skeletal muscle, and skin – as well as tumors-on-chips, which could lead to personalized cancer therapies.

## Virtual human-on-a-chip

While individual organs-on-chips hold enormous potential for understanding and testing organ-specific effects, the human body is more complex than what an individual chip can replicate. That's why researchers are working to link individual organs-on-chips into a virtual human. The goals are to gain new insights into disease and to predict how a drug will affect an individual organ *and* the rest of the body.



**Human-on-a-chip:** Researchers are working towards linking multiple organ-chips to more closely replicate human physiology body-wide. *Image reprinted from Trends in Cell Biology, 21/12, Huh D, Hamilton GA, and Ingber DE, From 3D Cell Culture to Organs-on-chips, 745-54, Copyright (2011), with permission from Elsevier*

The National Center for Advancing Translational Sciences at the National Institutes of Health, the US Food and Drug Administration, and the Defense Advanced Research Projects Agency are funding a number of projects to advance organs- and humans-on-chips. These groups and other international agencies have declared a lofty goal to build virtual humans-on-chips within a decade. Several groups already have successfully connected up to four different organs-on-chips that communicate with each other. Eventually, with continued development, it could be possible to create biochips made entirely from an individual's stem cells. That would be precision medicine at its best, understanding *your* specific disease and using *your* cells to determine the most effective therapy for *you*.

Today, organs-on-a-chip and the emerging human-on-a-chip technology represent a small subset of all cell types, tissues, and organs in the body. For studies where no organ-chip exists, or where the complexity of the interactions being modeled exceeds what technology can replicate, approaches such as animal research are our best option. But these chips have the potential to transform drug development and study of disease. 📌

*Author, Sylvia Wrobel; Scientific Advisors, Geraldine Hamilton, PhD and Scott Simon, PhD; Managing Editor, Anne M. Deschamps, PhD*

*Horizons in Bioscience* is a product of the Federation of American Societies for Experimental Biology (FASEB) and describes scientific discoveries on the brink of clinical application. These one page documents are intended to supplement our longer series of illustrated articles, *Breakthroughs in Bioscience*. Free hardcopies may be ordered and electronic versions of the full series may be found on our website: [www.faseb.org/breakthroughs](http://www.faseb.org/breakthroughs)