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.

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 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.

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.

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