HUMAN HEALTH
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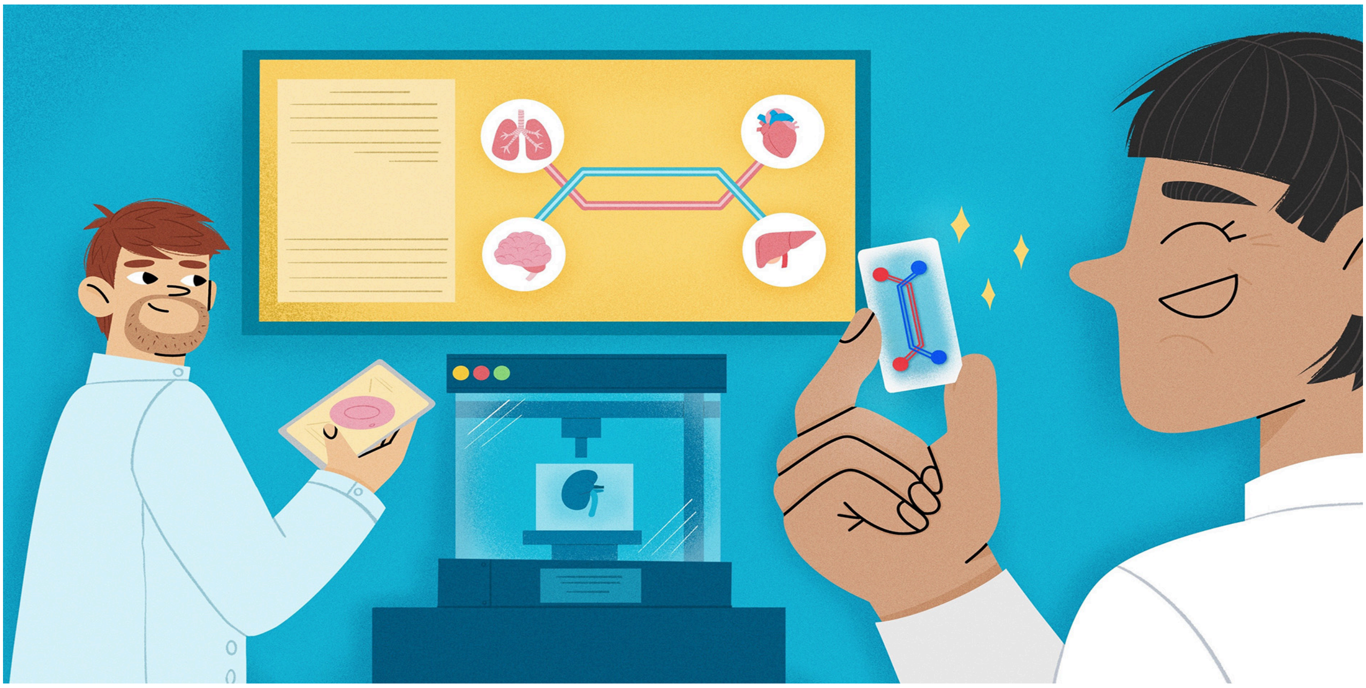

CREATING TINY HUMAN "ORGANS" TO TEST MEDICINES... AND MORE!

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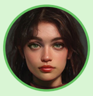
YOUNG REVIEWERS:



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AGE: 8

Scientists have developed tiny cell models called microphysiological systems (MPSs) that mimic human organs, allowing medicines to be tested without using animals. MPS contain human cells carefully arranged to simulate a real organ's structure and function. One type of MPS, called an organ-on-chip, also pumps fluids containing nutrients and oxygen through the model, similar to the function of blood flow in our bodies. These MPSs can test how medicines affect human cells and help scientists develop safer, more effective treatments for diseases. MPSs can also be personalized using a patient's own cells, to find the best treatment for each person. While challenges remain, like cost and reliability, MPSs are steadily improving. Beyond testing medicines, they can be used to study dangerous environmental chemicals and to model diseases. We can even connect multiple "organs" to simulate the whole body. As these revolutionary technologies improve and become widely

accepted, they could speed up drug development and reduce animal testing.

MIMICKING THE HUMAN BODY IN THE LAB

Have you ever wondered how scientists test new medicines to make sure they are safe and work well? In the past, medicines were often tested on animals, but this testing might not be enough, because humans have many differences from test animals [1]. This means that the results seen in animals might not be the same as what happens when humans take the medicines. As understanding of biology has advanced, scientists have found better ways to mimic the complex functions of human tissues and organs in the lab. These new technologies are called **microphysiological systems** (MPSs). MPSs have been designed to mimic the human gut, brain, or lungs, just to name a few. Scientists have found several creative ways to produce MPSs, including plastic scaffolds with cells "printed" onto them with cell-containing ink, organ slices, simple balls of cells that form in "drops" or in constantly stirred growth liquid, and more (Figure 1).

MICROPHYSIOLOGICAL SYSTEMS

Tiny laboratories that mimic the functions of human tissues and organs, allowing scientists to study biology and test medicines.

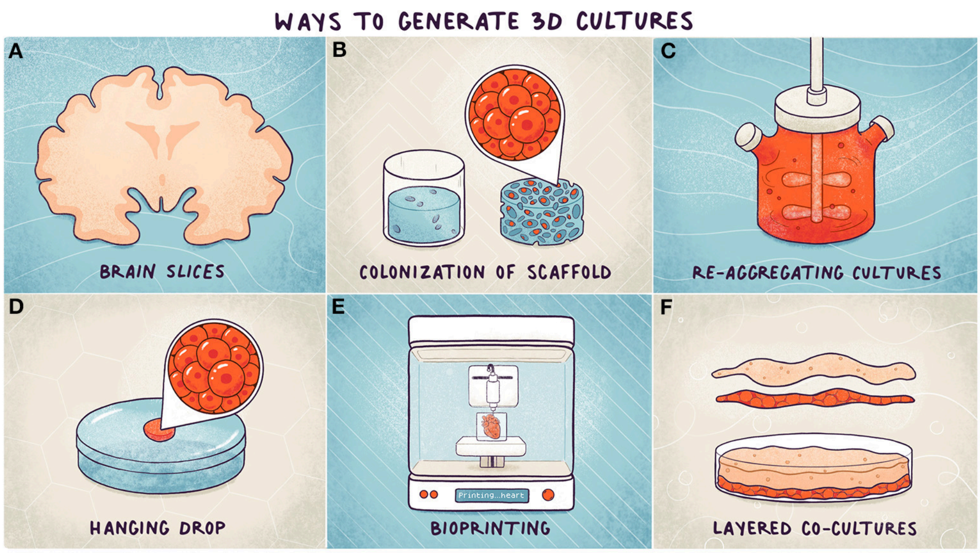

Figure 1

Figure 1

(A) Scientists can use parts of human organs (e.g., from surgeries or organ donations) to grow the cells in the lab. **(B)** Plastics or other materials can be used to give cells something to attach to. **(C)** Cells can be grown in liquid cultures that are stirred, so that balls of cells form. **(D)** Cells can be grown as hanging drops (picture a raindrop hanging from a leaf) so that cells collect at the bottom of the drop. **(E)** Bioprinters, in which the "ink" contains cells, can be used to "print" organs. **(F)** Layers of different cell types can be grown in culture dishes, for example to create model skin.

ORGAN-ON-CHIP: SIMULATING HUMAN ORGANS WITH BLOOD FLOW

One interesting new type of MPS is called an **organ-on-chip system**. These are tiny devices, approximately the size of a USB stick for a computer. Inside these chips, scientists carefully arrange various types of human cells and tissues to simulate the structure and function of a real organ, like the heart, liver, or lungs. They even include tiny blood vessels to simulate the flow of blood and nutrients. Organ-on-chip

ORGAN-ON-CHIP

A small device containing human cells arranged to simulate the structure and function of a real organ, like the heart or liver.

systems are like having tiny laboratories in which tissues and organs behave the same way they do in our bodies. They allow scientists test medicines or other substances to see how humans might react.

ORGAN-ON-CHIP SYSTEMS TO DEVELOP AND TEST NEW MEDICINES

While they are still a new technology, organ-on-chip systems (or other MPSs) may soon help scientists to develop safer and more effective medicines [2]. Scientists can test new medicines on these chips to see how human cells and organs might react, without endangering humans or animals. Not only might organ-on-chip systems be more accurate than animals for figuring out how human bodies might react, but the use of MPSs could also help to reduce the number of animals used in research.

Let us say scientists are working on a new medicine to treat a specific disease, like liver cancer, for example. They could use an organ-on-chip model of the human liver to test how the medicine affects liver cells, to see how the drug would behave in the human body. For instance, they could check to see whether the medicine has any **toxicity**, meaning dangerous side effects, before it is used in humans. Animal studies do not always identify side effects seen in humans. Scientists could also use an organ-on-chip system to test **efficacy**—how well the medicine works, for example to kill cancer cells. To do so, they could add some cancer cells into the chip's liver tissue and see what happens to the cancer when they treat the chip with the medicine. Overall, organ-on-chip systems can be used to assess the effectiveness of medicines in a realistic environment. They could help to make medicines safer, more effective, and could speed up the development process to make drugs for diseases like cancer, heart disease, and diabetes more accessible to people all over the world.

TOXICITY

The degree to which something, like a medicine or chemical, can cause harm or dangerous side effects in the body.

EFFICACY

How well a medicine or treatment works to produce the desired effect, like curing a disease or relieving symptoms.

GETTING PERSONAL—CREATING MODELS OF INDIVIDUAL PATIENTS

Another exciting prospect for MPSs is the potential to use them for **personalized medicine**. Everyone's body is unique, and the medicines or treatments that work for one person may not work the same way for another. Because they are built from human cells, MPSs can be used to personalize treatments. For example, with organ-on-chip systems, doctors could test new medicines on a patient's own cells and tissues before giving them to the actual person. This approach could help doctors find the best treatment for each individual, making healthcare more effective overall.

PERSONALIZED MEDICINE

Tailoring medical treatments to an individual patient based on their unique genetic makeup, lifestyle, and health needs.

CHALLENGES REMAIN

Shrinking entire organs down to fit onto tiny chips is a very difficult task. MPSs are still new technologies, so they are not perfect—a lot of challenges remain to be solved. One is cost. MPSs can be expensive to develop and to produce in large enough numbers for researchers to use them on a daily basis. Another lingering issue is **reproducibility**. A critical aspect of *any* experiment or scientific test is the ability to get similar results every time the test is run on the same sample. Reproducibility helps scientists and doctors trust test results and allows the test to be used in important processes like official approval of medications for use in humans. The complicated process of making sure a scientific test works the way it is supposed to and produces reproducible results is called **validation**. MPSs are still being validated, but they are getting much closer to being trusted by scientists and health experts. Scientists are working hard to overcome the remaining challenges with organ-on-chip systems and other MPSs.

REPRODUCIBILITY

The ability to get the same or similar results each time a scientific experiment or test is repeated under the same conditions.

VALIDATION

The process of thoroughly testing and confirming that a scientific method or tool, like an organ-on-chip, works correctly and produces reliable, reproducible results.

BEYOND TESTING MEDICINES

Organ-on-chip systems and other MPSs can be used for more than just testing medicines. They could also be used to test the effects that pollutants or toxins in the environment have on human cells and organs. For example, more and more children are diagnosed with autism and many researchers suspect that some chemicals contribute to this; brain MPS are increasingly used to test this idea. MPSs are also starting to be used for modeling diseases. For example, blood vessels-on-a-chip have been used to recreate blood clotting disorders seen in response to some medicines. A bone marrow-on-a-chip system can investigate the effects of anti-cancer treatments on blood cell development. Organ-on-chip systems can even be used to model rare genetic disorders, like cystic fibrosis, potentially paving the way for personalized treatments based on the individual's unique biology. In our lab, we used a brain MPS [3] to show for the first time that the virus that causes COVID-19 infects human brain cells [4], and to study how certain chemicals might result in brain-development problems such as autism.

Even more exciting, complex MPSs can be built to model the *interaction* of multiple organs (Figure 2). This is important because many of the body's complex processes involve more than one organ. For example, the liver can chemically change medicines, which is called drug metabolism, and this may change the effects that a medicine has on other organs. To better understand such interactions, researchers can connect different organ chips together, creating a kind of mini human-on-a-chip. For instance, combining liver, kidney, and intestine chips has been used to get a more accurate idea of how medicines will behave in the human body.

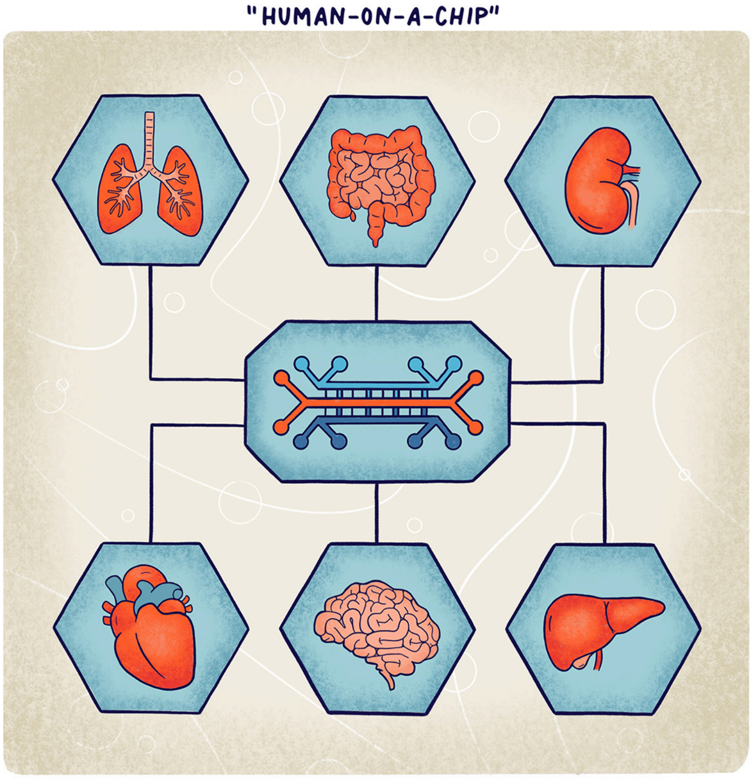

Figure 2

Figure 2

In the human body, organs do not work alone—they depend on each other. For example, the liver can convert a medicine into another chemical that might have different effects on the body. Increasingly, scientists connect various organ-on-chip systems to more accurately study processes in the whole body. These "organs" are connected by tiny tubes that deliver nutrients, oxygen, and other molecules, much like blood vessels. These technologies are called human-on-a-chip systems, and they can make testing new medicines even more accurate. However, figuring out the right laboratory conditions to allow all the organ chips to work together is quite challenging.

MOVING INTO THE FUTURE

In conclusion, MPSs such as organ-on-chip systems are a revolutionary advancement in drug development, as well as a promising way to study how the human body works in both health and disease. MPSs may prove to be more accurate than animal studies, helping scientists to develop safer and more effective medicines, and they could also save the lives of many research animals. We hope to soon see MPSs used more widely, particularly for testing new medicines. To help make this a reality, big important groups like the US Food and Drug Administration (FDA) have started working with companies and universities that make organ-on-chip systems and other MPSs. The FDA is also training its workers on how to use these technologies to evaluate the safety and efficacy of new medicines. In 2023, the US President signed the FDA Modernization Act, which urges the FDA to use MPSs and other alternatives to animal testing—so this should speed up the rate at which the FDA and others begin using these new technologies.

While scientists still cannot recreate every type of organ in the human body as an MPS, there are MPS for most organs now—and they get better every year. So, you will likely hear more about organ-on-chip systems and other MPSs. When you do, remember that they are like tiny laboratories that help scientists understand how our bodies function. They may be small, but they have the potential to make a huge impact on the development of new medicines and improve healthcare for everyone. Who knew so much could come from something so small?

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CONFLICT OF INTEREST: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

MEHRANEH, AGE: 15

Hi My name is Mehraneh, which means warm and loving like the sun. I really enjoy doing these reviews. I believe it will help me when I get to college and start my journey in the medical field. In my spare time I like to read, draw and paint. I also love babysitting little kids and teaching.

YISHENG, AGE: 8

With a keen interest in life sciences, astronomy, and mathematics, I love diving into books and immersing myself in the world of strategic games like Go (Weiqi), which sharpens my analytical thinking. Fencing is another passion of mine, as it strengthens my discipline, focus, and quick decision-making skills. I am committed to exploring the mysteries of life and the cosmos. My diverse interests guide me in unique approaches to scientific discovery.

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Dr. Smirnova is an assistant professor in the Environmental Health and Engineering Department at Bloomberg School of Public Health, and Center of Alternatives to Animal Testing, Johns Hopkins University (USA). Her research focuses on the development of new advanced cell-culture methods (microphysiological systems, MPS) that allow scientists to study the development of the brain without using animals. Her main interest is understanding the environment can interact with genetics and the consequences of those interaction for brain development. She received her Ph.D. from Charité Free University, Berlin and did her postdoctoral training at Federal Institute for Risk Assessment, Berlin. She is a co-organizer of a series of World Summits on MPS and a president of the International MPS Society.

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Thomas Hartung has spent more than three decades of his career promoting technologies to replace animal testing. From 2002 to 2008, he led the European Center for the Validation of Alternative Methods (to animal experiments) of the European Commission in Italy, and since 2009 he has led the Centers for Alternatives to Animal Testing in the US and Europe. He is active in many fields of science: he started by studying biochemistry, human medicine, and mathematics/informatics; he initially became a doctor (M.D./Ph.D.), and then a professor of both pharmacology and toxicology. He later expanded his work to include immunology, microbiology, and engineering. Today he holds five professorships at Johns Hopkins University and Georgetown University in the US and at the University of Konstanz in Germany. He is field chief editor of Frontiers in Artificial Intelligence. Aiming to bioengineer brain functions in human organoids, he steers a community of scientists to establish organoid intelligence. *thartung@jhsph.edu