Tel Aviv University's Ben Maoz, who works at the intersection of biology, chemistry, electrical engineering and neuroscience, displays an example of his lab's organ-on-a-chip technology, which allows researchers to study human physiology by mimicking the functionality of organs by putting living cells in clear silicone-based polymer chips

By Zac Unger
Photographs by Boaz Perlstein

OUT OF BODY EXPERIENCES

BEN MAOZ WANTS TO REVOLUTIONIZE DRUG DEVELOPMENT BY REPLICATING HUMAN ORGANS ON CHIPS

In 1996, the U.S. Food and Drug Administration approved 53 new medications. Two decades later, after massive advances in computing technology and artificial intelligence, new DNA editing and sequencing tools, and impressive advances in basic science, that number increased all the way to … 59. And those years were outliers on the positive end; the intervening period saw an annual average of just 30 drugs getting the official stamp of approval that paves the way for distribution to patients. Bringing a drug through that process can take well over a decade and cost upward of $2 billion USD. While drug companies might undertake this arduous path for a medication expected to be taken regularly by a wide swath of patients, research often ignores rarer (or less profitable) diseases.

Ben Maoz wants to change all that. His secret weapon is a clear piece of plastic about the size of a USB drive. Maoz, who held an Azrieli Early Career Faculty Fellowship between 2018 and 2021, is cross-appointed to the Department of Biomedical Engineering and Sagol School of Neuroscience at Tel Aviv University (TAU). Working at the forefront of biology and engineering, he and his colleagues mimic the functionality of human organs on what they call organ-on-a-chip technology.

"Between 60 and 90 per cent of drugs that successfully pass animal trials actually fail in human clinical trials," says Maoz. "At the end of the day, rodents are not humans. So what we are doing is using tissue engineering to create a human model that is not a human being." Each tiny organ-on-a-chip is loaded with actual human cells from a specific bodily organ, which are kept alive and functioning so scientists can apply experimental medications and monitor responses. "Animal models are simply not predictive enough," Maoz continues. "The best way to predict how human cells and tissues will react is to experiment with actual human cells and tissues."

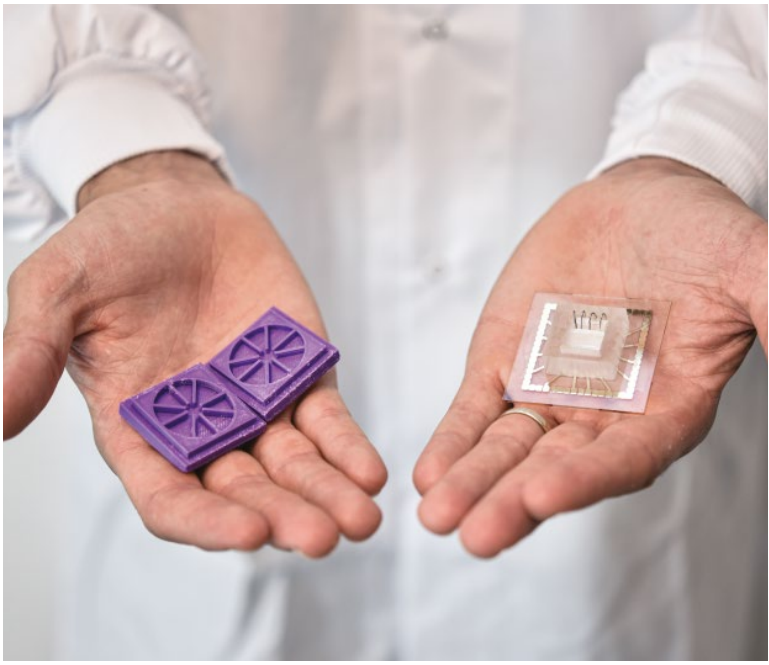
Maoz did his graduate work in chemistry at TAU and returned to TAU after completing a postdoctoral fellowship at Harvard University's Wyss Institute. It was at Harvard that he first visited a lab and saw the vast potential inherent in tissue engineering. "Wow," he said at the time, "this is it!" Today, Maoz's lab includes people with backgrounds in biology, chemistry, electrical engineering, neuroscience and even psychology. "What I'm looking for is a spark in their eyes," he says. "Because what we're building isn't just a buzzword or an idea — it's a tool that can help people in the real world."

As you can imagine, replicating the complexity of human physiology in an external model is an incredibly complicated proposition. Doing it affordably and at scale further increases the challenge. The chip is made of non-reactive silicone-based polymers and is designed with narrow channels running from one end to the other to mimic human vasculature, along which can be pumped blood, oxygen or pathogens.

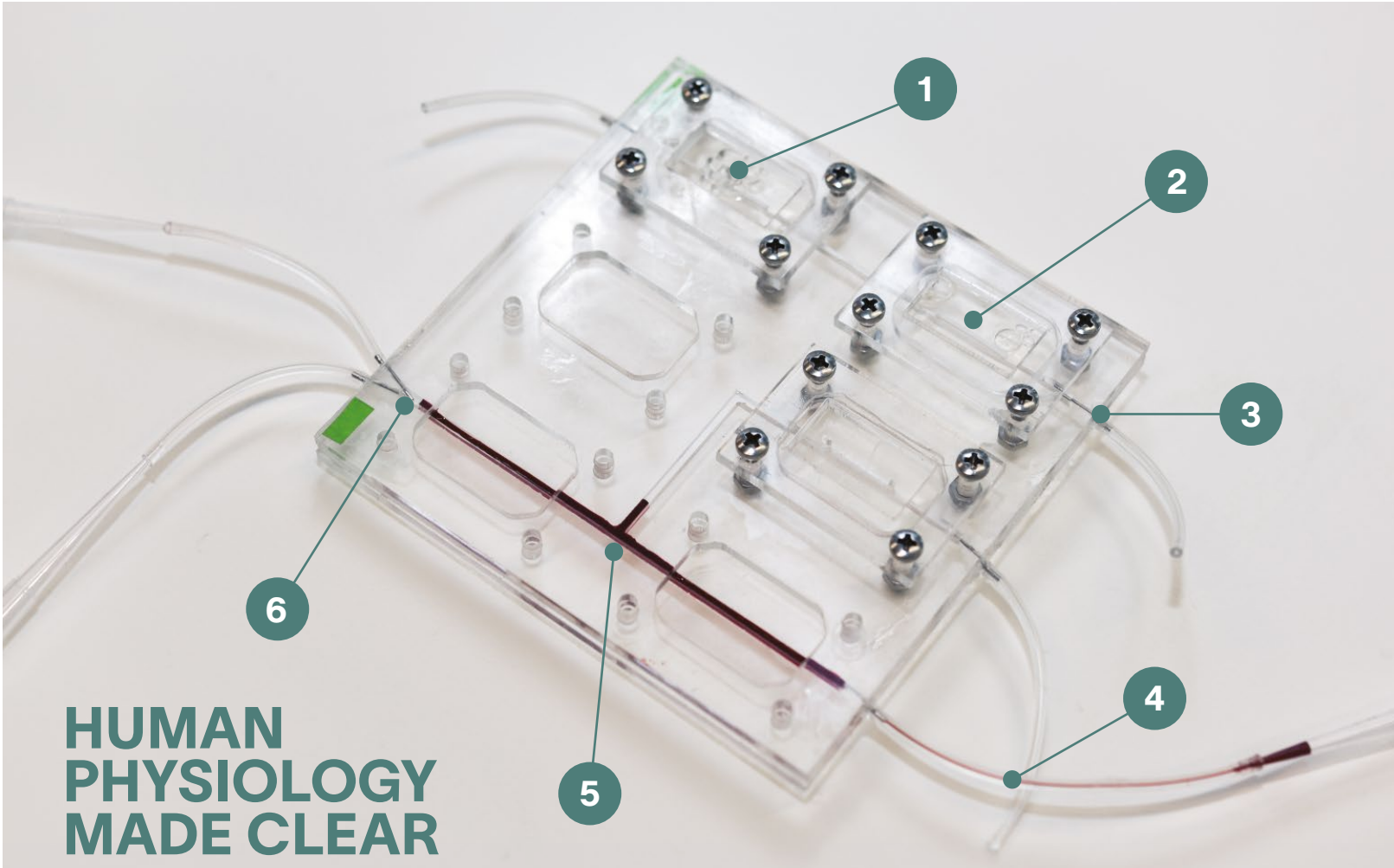
Scientists like Maoz receive cells from living donors, then culture these cells in incubators that carefully calibrate temperature and nutrient levels. Once introduced to the chip, the cells live under conditions very similar to those they would encounter in nature, as the constant flow is better representative of true conditions than the stasis of traditional glass slides. Cardiac cells on a chip will visibly contract, for example, just as they would inside the heart; lung tissue will stretch and push against the flexible silicone, as it does during inflation when people in inhale. One obvious advantage to this approach is that, unlike the human body, these chips are clear, making it easy for scientists to observe what would normally be the inner workings of an organ.

But the human body is far more complex than any single organ. The lungs are irrelevant without the heart, and nothing works unless the brain makes it happen. "In the lab we were able to build up to 10 different organs," says Maoz. "Each organ is basically like a Lego that we can click together to make a 'mini-me' on a chip."

In a breathtaking technical advance, Maoz and his collaborators linked eight different organs and kept them working as a system for 21 consecutive days. This linkage is vital for the testing of new pharmaceuticals because it's important to know not just the impact on the target organ, but any side effects downstream in the rest of the body. "When you take a pill," Maoz says, "it's absorbed in the gut, then is metabolized in the liver and eventually cleared by the kidney."



"What I'm looking for is a spark in their eyes," Maoz says about the students and collaborators he works with. "Because what we're building isn't just a buzzword or an idea — it's a tool that can help people in the real world."



HUMAN PHYSIOLOGY MADE CLEAR

1. An organ-on-a-chip, which can be loaded with actual human cells from specific bodily organs, such as the heart or lungs.
2. Made of clear non-reactive silicone-based polymers, chips can be linked to one another, allowing researchers to observe how the organs function as a system.
3. The outlet of the channel that links the chips, which mimics human vasculature and can carry blood, oxygen or pathogens.
4. An outlet carrying blood out of several linked chips; the blood can be analyzed to better understand how pathogens affect various cells.
5. A setup for connecting multiple chips. This system allows researchers to link up to six different "organs," which can work as a system for days and weeks.
6. The inlet of the channel, though which Maoz has been able to introduce drugs and observe their impact on different cells and tissues.

Each tiny organ-on-a-chip is loaded with actual human cells from a specific bodily organ, which are kept alive and functioning so scientists can apply experimental medications and monitor responses.

‘Right now, we give medicines to people based on a statistic, and 75 per cent of people are getting a drug that is not optimized for their condition. But imagine if I could test different drugs on your exact cells.’

Rapid Testing on a Chip

“Do you remember those first days of COVID?” Ben Maoz asks. “We were all sure that it was going to be like a zombie invasion, right?” While most people were sealing their windows and stocking up on canned goods, Maoz’s mind leapt immediately to the scientific challenges at hand. “I felt that I needed to contribute with the tools that I had,” he says, “to try to get a better understanding of what was going on with the virus.”

Because the virus itself was so dangerous to work with, requiring special approvals and engineering controls in the lab, Maoz hit on the idea of breaking the virus down into its component subunits, the 29 specific proteins that are the building blocks of SARS-CoV-2: “We wanted to identify which proteins had the largest effects on the vasculature.” Maoz cultured cells from a human umbilical vein and then transduced them with plasmids that coded for the various proteins. “And then we took it to the next level,” he recalls, “to model which tissues in the body would be the most susceptible to COVID.”

Looking back now, two years later, Maoz is impressed by how accurate his predictions were. “We saw that the lungs, the vasculature and the neurons of the brain were especially at risk,” he says, leading to the strokes, heart disease and brain fog reported by so many COVID-19 patients. While being “right” about a disease that has killed millions of people worldwide isn’t a happy occurrence, Maoz is gratified by the idea that his methods will allow for rapid testing of medications to alleviate the symptoms of people with long COVID and the lingering impacts of their initial infection.

To help test the organ-on-a-chip concept, Maoz looked at the impact of crystal meth. He could see exactly how the drug opens up the the brain's vasculature, exposing neural cells to toxins and placing them under stress. "We also saw that these effects were reversible," he says, "but only up to a point."

The most complex organ to model — and where Maoz is having the greatest impact in his field — is the brain. Because of its sensitivity, the brain is protected by a layer of endothelial cells known as the blood-brain barrier (BBB), which allows only select molecules to diffuse while blocking pathogens and harmful substances. This barrier, while protective, also makes it so difficult to deliver medications that many pharmaceutical companies have essentially stopped trying to create new medicines for diseases of the central nervous system. "It's a dual problem," says Maoz, "because you don't just need to find the drug that will treat the condition, you also need to find a way to penetrate and bring this drug to the brain."

Maoz designed a model with three chips: a brain chip with human neural cells, flanked on either side by BBB chips filled with microvascular endothelial cells. They then flowed artificial blood and cerebrospinal fluid through the first BBB chip to analyze influx to the brain. The second BBB chip became the reservoir for efflux, modelling the compounds that leave the brain. These linked cartridges can be induced to acquire a disease, then subjected to "human" drug trials without needing to use actual patients with Alzheimer's, Parkinson's or other ailments.

"Think about the companies that invest in projects where 90 per cent of the trials go to waste," Maoz says. "Imagine that you could bring that number down and then save them even just 10 per cent on a $2 billion project. The implications are enormous."

For proof of concept, Maoz experimented with one of the most destructive forces a human brain can encounter: crystal methamphetamine. "The first thing we saw was that meth opens up the brain's vasculature," he recalls. "It opens up the gates that should be keeping your brain safe," exposing the neural cells to toxins and debris even before the effects of the drug itself began to kick in. By observing the brain-on-a-chip, they were also able to see exactly how the drug placed the neurons under stress, driving them to ever higher levels of frenzied activity before suddenly causing them to crash.

"We also saw that these effects were reversible," Maoz says, "but only up to a point. If you do this over and over, the brain will not recover."

The potential health and societal ramifications of organs-on-a-chip are huge. "Right now, we give medicines to people based on a statistic, and 75 per cent of people are getting a drug that is not optimized for their condition," Maoz says. "But imagine if I could test different drugs on your exact cells, using personalized medicine to do a test on your tissue with your relevant physiology."

Maoz feels proud to be doing this work and appreciates how the Azrieli Fellows Program embraces young principal investigators at the challenging start of their careers. This early support enabled him to focus on science, rather than worry about funding, leading him to the unique spot he's in today.

"We are working with pharma companies to expedite drug development," he says. "We work with patients who need the world to develop something for their specific conditions. There was a company that just had a drug retracted by the FDA, and they were able to do experiments on the chip and find the exact point of failure and get the process back on track." ▲●■