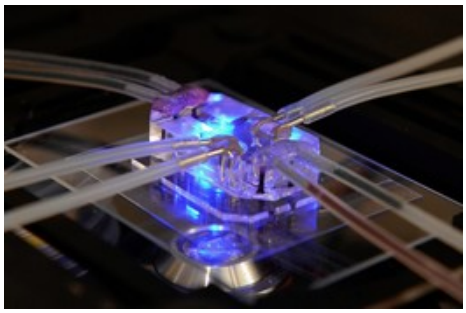
THE WALL STREET JOURNAL.
WSJ.com

NEXT IN TECH | June 18, 2013, 12:14 a.m. ET

Forget Lab Rats: Testing Asthma Drugs on a Microchip

By JONATHAN D. ROCKOFF

Forget lab rats. Some researchers are now testing medicines on a silicon chip that could provide a better read on how a drug will work.



Wyss Institute

A chip engineered to replicate a human lung.

A Closer Look

Video: See How the Chip Works

Source: Wyss Institute for Biologically Inspired Engineering at Harvard University

These scientists are building "organs on a chip," spooling together the important cells that make up, say, a lung, and then mimicking the key functions of the organ. Then researchers test to see what kind of impact a potential drug has on this lung-like system, created on a chip that is only a few inches long.

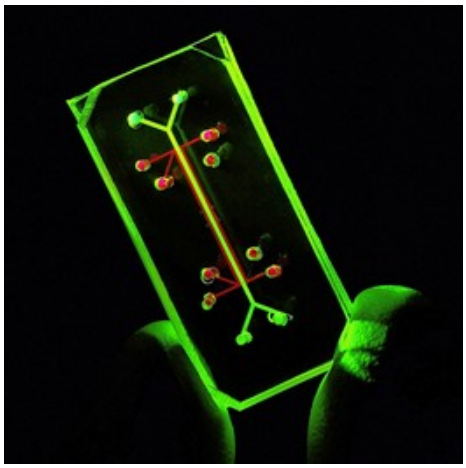
Companies are starting to tinker with this new technology, mostly for internal decision-making, since health regulators haven't yet authorized their use in decisions about whether a compound can enter human testing.

At Merck & Co.'s labs in Boston, researchers are looking at using microchips engineered to resemble a diseased lung in their hunt for a new asthma treatment.

Company scientists want to see whether these "lungs on a chip" can help them better understand the biology behind asthma and identify promising candidates for medicines, says Don Nicholson, who oversees Merck's respiratory drug research.

If efforts like Merck's pan out, drug makers could have a powerful new tool, and avoid wasting millions of dollars chasing compounds that will flame out.

The lung on a chip demonstrates the feasibility of the concept, says Christopher Austin, director of the National Center for Advancing Translational Sciences, a part of the National Institutes of Health that's helping fund projects to replicate a variety of tissues and organs.



Wyss Institute

The chip is illuminated by green light.

"Ultimately we're going to have a 10-organ system we put together," says Michael Shuler, chairman of Cornell University's biomedical engineering department.

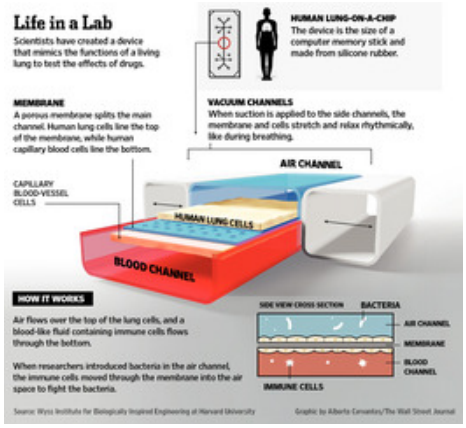
For now, the technology is a work in progress. Regulators aren't ready yet to scrap the need for animal testing or other current methods for determining whether a promising molecule seems safe and effective enough to move into testing in patients.

Drug makers are still vetting the initial entries, while various laboratories try to develop chips mimicking the function of the kidney, liver and other organs.

"There's a lot of additional work that's needed before these systems can replace our current methods to evaluate a drug's safety or effectiveness. The potential is there, however," says Douglas Throckmorton, deputy director for regulatory science at the FDA's drug division.

The lung on a chip doesn't recreate everything a lung does, but replicates many of the important functions. It consists of a see-through strip of silicone rubber about the size of a memory stick, with tiny, hollow channels through which air and fluid can pass. These channels are split by a flexible membrane, whose sides are lined by walls of human lung tissue and blood-vessel cells.

Like in breathing, the walls of cells can relax and contract, thanks to the application of suction. As in a living lung, air flows over the human lung cells lining one side of the membrane, while a fluid mimicking blood passes by the capillary blood vessels on the other side.



Researchers at Harvard University's Wyss Institute for Biologically Inspired Engineering, which unveiled the lung on a chip in 2010, infected it by sending bacteria past the lung cells and then watched the immune cells flock to and then attack the bacteria as happens in the real organ.

Likewise, the researchers afflicted the lung on a chip with a condition, known as pulmonary edema or fluid on the lungs, that makes breathing difficult.

"You actually mimic complex organ responses," says Donald Ingber, the Wyss Institute's founding director.

Working with the institute, drug maker GlaxoSmithKline PLC tested a potential drug's effect on the diseased human lung on a chip, and found that it replicated the response seen in dog, mice and rat models of pulmonary edema.

GlaxoSmithKline is now exploring how to use the device to assess the safety and efficacy of other respiratory compounds, says Kevin Thorneloe, a senior Glaxo scientist.

Such validation raises hopes that organs on a chip could improve drug discovery. Only one out of

10,000 compounds discovered in a lab will eventually receive approval for use in patients, typically after more than a decade of R&D and tens if not hundreds of millions of dollars in investment, according to studies.

The limitations of animals as stand-ins for human patients are a major reason. Animal disease doesn't faithfully replicate asthma, for instance. The condition is uniquely human, says Merck's Dr. Nicholson, and animal models can't capture the constriction of airways and all of the other characteristics of the disease.

"We have found great mechanisms that can control asthma in an animal," he says. "And most of them have failed" in humans.

Merck aims to configure the lungs on a chip to resemble the lungs of some patients genetically predisposed to asthma, Dr. Nicholson says.

The company wants to explore the biological differences between these diseased lungs and healthy ones.

Merck also wants to probe the effects that potential drug mechanisms might have on the diseased lungs.

AstraZeneca PLC's neuroscience unit is in talks to use a liver microchip, made by closely held Hurel Corp., for some testing to see how quickly a molecule gets metabolized, says Doug Burdette, an AstraZeneca research project leader.

Such information is helpful when figuring out what kind of dose would be needed for the compound to provide a benefit and avoid unwanted side effects.

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