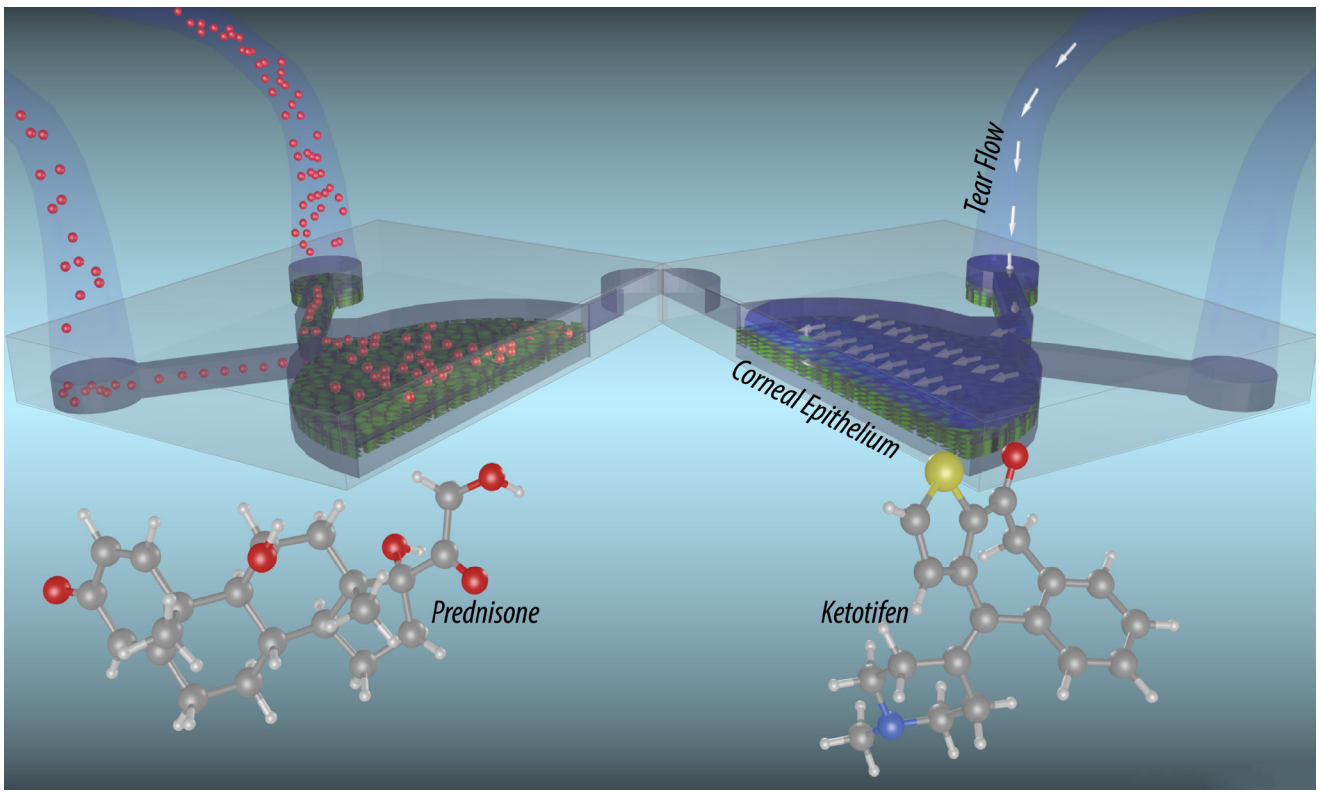
Research highlight

Microengineering ophthalmic drug testing

by Maxine Lipner EyeWorld Senior Contributing Writer



A schematic of the microengineered human corneal epithelium-on-a-chip. By recapitulating the multilayered cornea structure and tear flow profiles, this cornea chip enables physicians to determine pharmacokinetic properties of various ocular drugs more easily.

Source: Jungkyu Kim, PhD

Creating a cornea-on-a-chip

When it comes to studying new ophthalmic drugs, the mainstays of research have usually been the use of rabbit eyes or static Transwell cell culture insert technology. But to help improve accuracy and lower costs, researchers have developed a new approach dubbed a microengineered human cornea-on-a-chip,[1] according to **Jungkyu (Jay) Kim, PhD**, assistant professor, Department of Mechanical Engineering, Texas Tech University, Lubbock, Texas.

Current approaches do not mimic the actual eye's condition since they do not include a tear film or tear flow, according to Dr. Kim and his team, collaborating with **Tim Reid, PhD**, at Texas Tech University. With the static Transwell technology, a drop of drug is placed on top, allowed to stay there for awhile, then another look is taken to see how much of the medication has penetrated to the bottom. Likewise, there are issues with the rabbit corneal epithelial layer, which is a bit thicker than that of humans and as a result doesn't give accurate values.

Because of this, Dr. Kim set out to develop a device that could simulate what happens on the cornea when drugs are administered. He created a first-of-its-kind cornea-on-a-chip, in which human corneal epithelial cells are cultured on a porous membrane embedded on a microfluidic platform. This not only mimics the human corneal structure and includes tear flow patterns, but also takes blink rate associated with this into account. "By incorporating the pulsatile tear flow, we could investigate how much impact there is on pharmacokinetics and pharmacodynamics of topical ocular medications," Dr. Kim said.

Structural keys

One of the tricky parts in the process has been making proper substrate for the different corneal epithelial layers, Dr. Kim explained. Below this is the basal membrane, so this has meant knowing the topological and mechanical properties and properly mimicking this structure. "Otherwise the cell phenotype can be altered," Dr. Kim said. "Then we added the multilayer of the corneal epithelial cell on top." The investigators are now working on developing the stromal layer as well.

Incorporating blinking in the model was key. "For the blink rate, we got the proper frequency of how fast humans blink," Dr. Kim said, adding that they applied the pulsatile flow model on the microfluidic chip, which includes multiple ports to support the cell as well as to inject a tear flow to simulate drug clearance. This includes a well where the eye drop is placed. "We keep pumping the tears like the pulsatile flow," he said. Investigators considered how much of the drug penetrated through the cell layers and how much was released over time, Dr. Kim said.

Chip impact

In Dr. Kim's view, this could help speed the ophthalmic drug development process since it would allow for the simultaneous testing of many different types of ocular drugs. Dr. Kim thinks this will help practitioners to determine what happens with the drug simply by making a change in a small molecule or a functionary group.

Drug testing cost would also go down, Dr. Kim pointed out. He cited the fact that the synthetic chip is far less expensive than the animal eye. Also, the faster turnaround time would allow companies to arrive at an answer sooner, he noted, adding that the answers will be even more precise. "With the animal eyes you can't get the exact engineering value," he said. "By using this chip, we can get those numbers, and that would be a big help to a computational biologist."

Another application of the chip is in studying regenerative wound healing. Dr. Kim noted that one interesting facet of the cornea is the fact that you can scrape it many times a day and it still quickly heals. "A corneal epithelial cell itself has healing function," he said. "On top of that, the limbus where the border of the cornea and the sclera is has stem cell function." With the chip, investigators are working to gain insight into what the triggering molecule is that causes the limbus stem cell-like epithelial tissue to migrate into the scar area, Dr. Kim explained.

Likewise, they can examine the emergence of keratitis among contact lens users. Since the chip is clear, this enables investigators to visualize what is occurring. The fact that this is composed of soft material allows investigators to mimic the contact lens environment. "We're studying how the bacteria landed on the surface of the cornea and seeing how they propagate," Dr. Kim said. It is still widely unknown how they manage to dissolve the corneal epithelial layer and penetrate through this.

Dr. Kim estimated that this cornea-on-a-chip is about 5 years away from fruition. "We're pushing the limits, and hopefully we can give critical help to the ophthalmologist as well as the patient," he said. **EW**

Reference

1. Bennet D, et al. A microengineered human corneal epithelium-on-a-chip for eye drops mass transport evaluation. *Lab Chip.* 2018;18:1539–1551.

Editors' note: Dr. Kim has no financial interests related to his comments.

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