

## GLAUCOMA

# Novel Approaches to Drug Delivery

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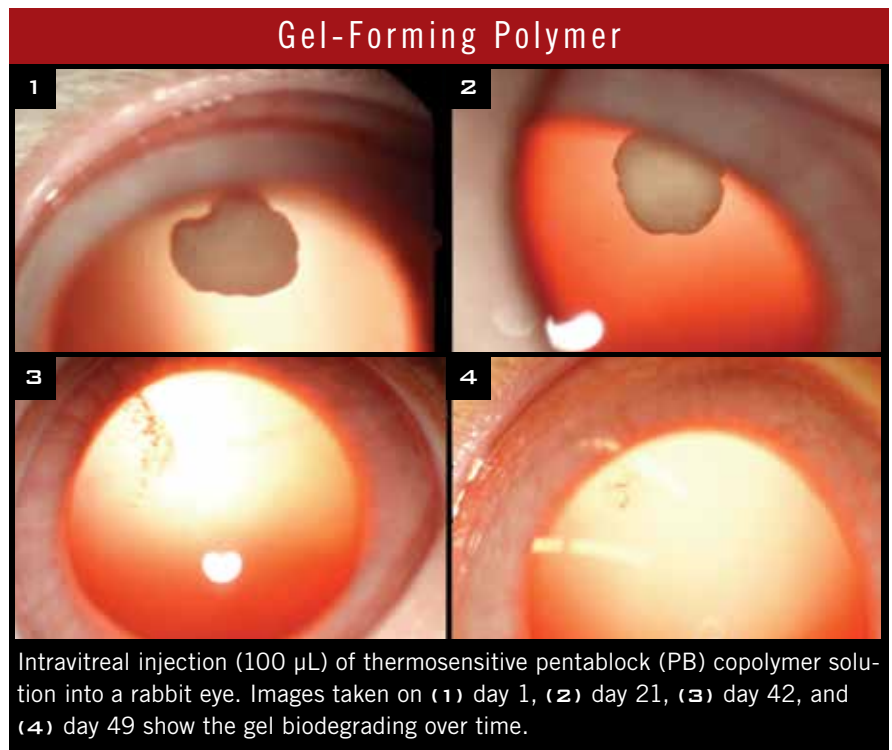
INTERVIEWING LOUIS B. CANTOR, MD, ANDREW G. IWACH, MD, ASHIM K. MITRA, PHD, AND GARY D. NOVACK, PHD

If only glaucoma patients would take their drops. But poor compliance is a problem as chronic as the disease itself, with reports of nonadherence to therapy running as high as 60 percent.<sup>1</sup> “The reason why most patients fail medical therapy is not because the drugs don’t work; it’s because patients can’t use them,” said Louis B. Cantor, MD, at Indiana University.

And compliance is only part of the problem—eyedrops have inherent limitations. Their volume ranges from 20 to 50  $\mu\text{L}$ , but the precorneal space holds only 7  $\mu\text{L}$ , explained Gary D. Novack, PhD, president of Pharmacologic Development. The excess either rolls down the cheek or exits through the nasolacrimal duct. About 1 to 5 percent of an applied drug is absorbed into the eye, with most of that staying in the anterior segment, he said.

But just getting the drug through the cornea is not the main problem, according to Ashim K. Mitra, PhD, at the University of Missouri–Kansas City; rather, “we need to have IOP pretty much under control all the time.” Achieving 24-hour control might require a higher concentration of the drug or a combination of drugs. The former may lead to systemic effects, while the latter can be a barrier to compliance, he said.

“Drug delivery continues to be an ongoing challenge,” said Dr. Cantor. “There’s a huge unmet need in terms of relieving patients of the burden of instilling drops.”



Intravitreal injection (100  $\mu\text{L}$ ) of thermosensitive pentablock (PB) copolymer solution into a rabbit eye. Images taken on (1) day 1, (2) day 21, (3) day 42, and (4) day 49 show the gel biodegrading over time.

### The Challenges

Systems to deliver medication predictably over time are not new to ophthalmology. Examples include the ganciclovir Vitrasert in the 1990s and the current intravitreal steroid devices. And even earlier, in the 1970s, the Ocusert Pilo system was approved for treatment of glaucoma; this extended-release device was designed to deliver pilocarpine over seven days. The patient inserted it under the eyelid into the lower conjunctival cul-de-sac and replaced it weekly. Dr. Mitra said that although this device controlled IOP, patients didn’t like it. It sometimes

moved, became displaced, and required manual dexterity to put it back where it should be, he said. It is no longer sold.

Why hasn’t there been anything since for glaucoma? “That’s a complex answer about invention, investment, and business factors,” Dr. Novack said. On the invention side, he described the challenge of creating something to treat a disease that requires chronic therapy. “There is limited space in the eye. So the size of a drug delivery system is limited by the duration of treatment, the potency of the molecule, and its duration of action. A low potency,

rapidly metabolized drug intended for a long duration, of say six months, would not ‘fit’ into the eye.”

### What’s in the Pipeline?

Nevertheless, several companies are investing in devices to overcome the challenges. A number of these novel approaches were outlined in a 2012 presentation by Andrew G. Iwach, MD, of the Glaucoma Center of San Francisco.<sup>2</sup> Beyond their possible use in glaucoma therapy, many of these technologies are being investigated for other applications as well, through sustained delivery of antibiotic, anti-inflammatory, or anti-VEGF drugs.

### Punctal Plugs

Dr. Cantor said that punctal plugs are “very promising” as a way to deliver glaucoma drugs. The plugs are inserted into the tear ducts, where they’ll stay for at least two to three months. “In theory, it’s a very elegant, simple approach to medical treatment that removes the compliance burden.”

Dr. Mitra agreed. “A drug-loaded punctal plug would be very useful.” He said plugs have been made of different polymers, including silicone, hydrogel, and a biodegradable polycaprolactone. “I like one that’s biodegradable as it elutes,” Dr. Mitra said. “Then you put in a new plug with a new dose.”

There are some challenges, however. One is that the plug is a foreign object with the potential to move, cause irritation, and fall out, Dr. Mitra said. Movement can also affect drug release. He explained that if the plug moves, changes in the environment, including tear fluid and enzymes, can cause it to malfunction. Also, there’s a potential for bacterial buildup, so a preservative, such as BAK, needs to be added in the formulation to prevent infections. Finally, the plug should be able to release the drug at a constant rate over months, ideally up to six months.

At least two companies are actively developing punctal plugs for glaucoma treatment.

**Ocular Therapeutix.** This company is developing drug-eluting polyethylene glycol hydrogel plugs to deliver

three different types of medications: anti-infectives, corticosteroids, and the antiglaucoma drug travoprost. The OTX-TP2 delivers travoprost to the ocular surface for two to three months, then resorbs and passes out through the nasolacrimal system. The plug also contains fluorescein so that the clinician can monitor its retention.

Results of a phase 2 pilot study, involving 36 eyes of 20 South African patients, were reported in October 2012. Baseline IOP was between 24 mmHg and 34 mmHg (mean, 28.7 mmHg). Mean IOP decreased by 6.8 mmHg over two months, results that are comparable to effects of topical prostaglandin analogues ([www.ocutx.com/us/pipeline/prostaglandin-punctum-plug/](http://www.ocutx.com/us/pipeline/prostaglandin-punctum-plug/), accessed Oct. 22, 2013).

**Mati Therapeutics (QLT).** Also in October 2012, QLT reported that two phase 2 clinical studies demonstrated positive trends on the efficacy and safety of a latanoprost punctal plug delivery system in subjects with open-angle glaucoma and ocular hypertension. The studies assessed two different delivery doses as well as use of plugs in the upper vs. lower punctum or in both puncta simultaneously. In April 2013, Mati Therapeutics bought QLT’s punctal plug technology and plans to advance to phase 3 in 2014. ([www.qltinc.com/newsCenter/2012/121025.htm](http://www.qltinc.com/newsCenter/2012/121025.htm), accessed Oct. 22, 2013).

### Gel-Forming Drops

One approach that sidesteps the “foreign object” problem is an eyedrop that forms a long-lasting gel incorporating a drug.

**Pentablock copolymer.** Dr. Mitra recently patented a biodegradable pentablock copolymer that can serve as a vehicle for topical—for example, paired with a glaucoma drug—or intraocular drug delivery (Figs. 1-4). The five polymer blocks are all FDA approved for use in the eye.

For the topical version, it works like this: Put the drug in the polymer drop, which is not viscous. As soon as it touches the eye, it reacts with body temperature and transforms from a solution to a gel that cannot be

washed away. (Gelling might occur in the bottle at temperatures above 35 to 37 C, but it will revert to liquid after a few minutes at room temperature.) It forms a film under the lid, where the drug is released over time, while the polymer eventually degrades. The time course could be two, four, or six months, depending on the drug dose.

Dr. Mitra said that it’s difficult to create a polymer strong enough to hold a drug for slow release. Many polymers succumb to a “burst effect,” rapidly releasing 30 to 40 percent of the drug in a short time. The pentablock copolymer has proved resilient, he said. Another advantage is that the five polymers can be reconfigured to work with specific drugs. “We can make the polymer to suit the drug,” Dr. Mitra said. Though it hasn’t been tested, it’s possible to add the pentablock copolymer to latanoprost or timolol, he said. “We have used the polymer for other purposes, but I think we can do that for the front of the eye,” he said. “Now we need to study the right combination of drug and delivery system.”

Dr. Mitra envisions a time when we can tailor drugs to the patient by making the polymer to fit the individual’s dose. “Right now you give the same dose to everybody.” But what if you could titrate to the particular rate of release needed for the individual patient and maintain it for six months? The pharmacist dispenses. The patient puts it in a dropper, then into the eye, “and forgets about it.”

**InSite Vision.** Another gel-forming drop is InSite’s ISV-215. Dr. Novack described it as “a thicker drop that remains in the cul-de-sac longer.” It is composed of 0.03 percent bimatoprost formulated in a vehicle called DuraSite, which forms a stable mucoadhesive matrix to maintain contact with ocular tissues including the cornea and conjunctiva. The system can be customized to deliver a variety of drugs; it has already been approved for two classes of antibiotics marketed in the United States. An ARVO 2013 poster presentation reported that ISV-215 significantly improved bimatoprost delivery to rabbit eyes compared with

Lumigan 0.03 percent ophthalmic solution ([www.insitevision.com/pdf/ISV\\_215\\_LB\\_ARVO\\_2013.pdf](http://www.insitevision.com/pdf/ISV_215_LB_ARVO_2013.pdf), accessed Oct. 22, 2013).

**Injectables and Implants**

**Icon Bioscience.** IBI-60089 for glaucoma is a biodegradable product intended to deliver latanoprost to the anterior chamber for six months with a single injection through a 30-gauge needle. The vehicle degrades and eventually disappears as the active agent is released over time. The company announced plans to initiate a phase 1/2 clinical trial in the first quarter of 2014.

**psivida.** This company has already developed two approved sustained-release intravitreal devices, Iluvien and Retisert. Now, in conjunction with Pfizer, it is developing Durasert, a bioerodible drug delivery system for latanoprost that is injected into the subconjunctival space with a 25-gauge needle. A phase 1/2 clinical trial is currently underway ([www.psivida.com/products.html](http://www.psivida.com/products.html), accessed Oct. 22, 2013).

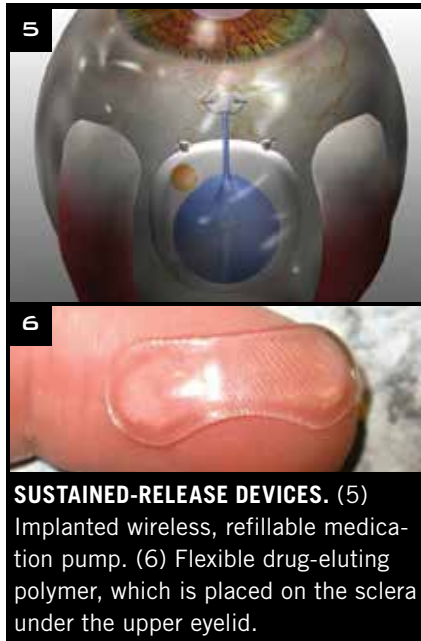
**Replenish.** The Ophthalmic Micro-Pump, implanted in the sclera, is being developed in glaucoma and retinal disease versions (Fig. 5). It injects programmed amounts of a drug at set times for up to 12 months; when the medication is exhausted, the device can be refilled with a 31-gauge needle ([www.replenishinc.com](http://www.replenishinc.com), accessed Oct. 22, 2013).

**Euclid Systems.** Two collagen-based systems are being developed by Euclid to provide sustained release of latanoprost: an injectable, in situ gelling collagen solution; and a 2 mm x 4 mm collagen wafer that is implanted in the sclera. The latter has demonstrated release of latanoprost for up to 180 days.

**Drug-Eluting Contact Lenses**

A group at the Massachusetts Eye and Ear Infirmary has reported success with a prototype contact lens that has widespread applications for sustained ocular drug delivery.<sup>4</sup> Dr. Mitra said it is being tested with latanoprost.

And Amorphex Therapeutics has created polymers that incorporate



**SUSTAINED-RELEASE DEVICES.** (5) Implanted wireless, refillable medication pump. (6) Flexible drug-eluting polymer, which is placed on the sclera under the upper eyelid.

drugs, including prostaglandin, timolol, and brimonidine. The company shapes these polymers into a clear, flexible device that is placed on the sclera, under the upper eyelid (Fig. 6). Although this device rests completely on the sclera, not the cornea, it incorporates some elements used in contact lenses, such as base and peripheral curvature and edge design for better fit and stability on the eye. It can hold a larger volume of drug than some of the other approaches. The company reports that its ocular insert prototypes have been worn successfully for more than 120 consecutive days, and in vitro drug release studies demonstrated consistent drug release profiles over many months (<http://amorphextherapeutics.wordpress.com/our-technology/>, accessed Oct. 22, 2013).

**What Lies Ahead**

Beyond improving delivery of existing drugs such as prostaglandin analogues, “We can leverage these new technologies to other molecules that are in the pipeline,” said Dr. Iwach. For example, these devices might open the door to drugs that have been sitting on the shelf because they couldn’t be used in a standard drop formulation owing to their pharmacokinetics or side effects at peak levels.

He even foresees a time when a nov-

el delivery system is coupled with an IOP-monitoring device. For example, Sensimed Triggerfish, a contact lens device, is capable of continuous IOP measurement,<sup>5</sup> and implantable wireless IOP sensors are also being developed. Dr. Iwach said that these developments hold the promise of linking a customized delivery system to a sensor, a concept similar to a closed-loop insulin pump. “For example, if data from an implanted monitoring device indicate that pressures are high only at night, an integrated device would then deliver medicine at night, when it’s needed,” he said. “That’s the future.” ■

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 3 Tamboli V et al. *Colloid Polym Sci.* 2013; 291(5):1235-1245.  
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