GLAUCOMA PIPELINE DRUGS
TARGETING THE TRABECULAR MESHWORK
No new class of drugs has come to market for treating glaucoma since 1996, when the FDA approved the first prostaglandin analogue, latanoprost (Xalatan). That could change soon: Experts who follow drug development are hopeful that we’re on the brink of reaping the benefits of years of research.

“It’s been a decade and a half and counting since we’ve had a new class of drugs to treat glaucoma. We’ve had formulary improvements and fixed combinations, but no novel agents,” said Louis B. Cantor, MD, at Indiana University. “We’ve gone through a long dry spell but are just beginning to see, in the last couple of years, exploration by pharma of some new types of drugs.” But, he added, “We don’t know how well those will pan out.”

The uncertainty about “panning out” involves both drug efficacy and marketplace issues. As Dr. Cantor said, “Prostaglandin analogues are pretty effective. For a company to go into the investment of developing a new class of drugs for glaucoma, they have to be better than prostaglandin analogues.”

Andrew G. Iwach, MD, at the University of California, San Francisco, agreed: “This is a unique time period for glaucoma medications in that we have very good drugs, usually well tolerated. And they’ve gone generic. That’s important, because having such strong generic contenders out there makes it harder for drug companies to try to introduce new molecules into this arena. Specifically, the prostaglandin analogues have set a high bar. It’s hard to compete with them.”

Given this barrier, what are the marketplace incentives for development? Sheer numbers, for a start: Ten thousand people a day turn 65, and this rate will continue for 18 years, Dr. Cantor said. “The number of people who are going to need treatment for glaucoma has already begun to increase substantially.”

Even more important, “Despite all the advances, our medical therapy fails not only for compliance reasons, but just fails,” Dr. Cantor said. “We need to continue to have new alternatives for treatment that are more effective, that last longer, and that have simple dosing requirements.”

Thus, any new drug that makes it from the bench to the clinic will be a welcome addition.
“Obviously, we want new and better therapies. We still have no cure for glaucoma. And while half of all patients are treatable with one drug, half are not. So we still need additional therapies to treat glaucoma,” said Gary D. Novack, PhD, president of Pharmalogic Development.

**Homing In on the Trabecular Meshwork** Finding drugs with new mechanisms of action could help fill that need. The currently marketed drugs reduce inflow of aqueous humor or increase outflow via the uveoscleral pathway, said Dr. Cantor. “We’ve by and large not been treating trabecular outflow.”

“We’ve always wanted to manipulate the trabecular meshwork [Fig. 1], but we’ve never been able to,” said Douglas J. Rhee, MD, at Case Western Reserve University. Now, after years of methodical research into the functioning of the trabecular meshwork, that goal is within reach, he said. Dr. Rhee leads a molecular biology laboratory that studies aqueous humor drainage.

In adults, about 80 to 90 percent of outflow works its way through the trabecular meshwork, the eye’s primary outflow pathway, Dr. Rhee said. He added that the only place where we can find a difference, pathologically, between people with and without glaucoma is in the trabecular meshwork. The trabecular outflow system of people with glaucoma is compromised (Fig. 2).

Rho kinase (ROCK) inhibitors and adenosine agonists are the two most-talked-about new classes of drugs. Physiologically, they make sense. “These two new classes directly target where the problem is—aqueous humor trabecular outflow,” Dr. Cantor said. “And glaucoma, with elevated IOP, is a trabecular disease.”

**Back to the future?** Targeting trabecular outflow isn’t an entirely new approach. The older drug pilocarpine did so indirectly, by causing the ciliary muscle to contract, which enhanced aqueous outflow, said Paul L. Kaufman, MD, at the University of Wisconsin School of Medicine and Public Health. This ciliary body contraction distorts the trabecular meshwork and Schlemm’s canal, facilitating fluid egress through the trabecular meshwork. Despite its ocular and systemic adverse effects, and the fact that it has to be used multiple times a day, pilocarpine remained a mainstay treatment for many years, said Dr. Kaufman. “As a topical agent, it was really all we had.”

**Rho Kinase Inhibitors** The ROCK inhibitors now in development differ from pilocarpine in that they work directly on the trabecular meshwork, Dr. Kaufman said (Fig. 3). “They relax the cells of the meshwork and inner walls of Schlemm’s canal. Functionally, they uncouple actin from myosin, two proteins that interact to contract ciliary muscle.” By inhibiting Rho kinase, for example, you reduce actin-myosin contractility, and the cells relax. “By a mechanism that is not entirely understood, this allows fluid to get through the pathway more readily.”

**How ROCKs work.** Rho kinase is a serine/threonine kinase that serves as an important downstream effector of Rho GTPase. It plays a critical role in regulating the contractile tone of smooth muscle tissues in a calcium-independent manner. Preclinical studies have found that modulating Rho kinase activity with-

**AQUEOUS PATHWAYS.** (2A) Normal aqueous flow passes through the TM (red arrow) and uveoscleral pathway (green arrow). (2B) In open-angle glaucoma, aqueous flow through TM is impaired without obvious blockage.
in the aqueous humor outflow pathway could lower IOP. In animal models, ROCK inhibitors reduced IOP by enhancing aqueous humor drainage through the trabecular meshwork.

Dr. Rhee explained that ROCK inhibitors are thought to work on the cell cytoskeleton of the juxtacanalicular region, which includes not only the trabecular meshwork but also the cells adjacent to the inner wall of Schlemm’s canal. According to this hypothesis, they shrink the cells, which creates space between the cells where fluid can exit.

Dr. Rhee used a bricks-and-mortar analogy to help explain what he thinks is happening. In his analogy, the cells of the inner wall of Schlemm’s canal are bricks. And the extracellular matrix is the mortar that holds the bricks together. “Think of a brick wall,” he said. “If you want water to get to the other side, you put holes in the mortar so water can get through.”

**ROCK research findings.** The ROCK inhibitors have been demonstrated to work in clinical studies. In phase 2 trials, conjunctival and episcleral vascular dilation and hyperemia (Fig. 4) were common side effects resulting from relaxation of episcleral vessels. These effects may be analogous to the purported mechanism of trabecular meshwork relaxation, Dr. Kaufman said. “For some trials, it [hyperemia] was a showstopper,” he said, adding that it may not be as significant in other trials because different molecules have different specificity. “It remains to be seen whether hyperemia will be a problem. It was with prostaglandins early on. Then scientists engineered a molecule to have more of the IOP-lowering effect and less of the blood-vessel-dilating effect. That’s where Xalatan came from.”

Although ROCK inhibition may be a good approach, and a couple of Rho kinase inhibitors have demonstrated effectiveness, Dr. Rhee said that he is “a little disappointed” with the modest effects reported in early trials. “I really thought that this class of drugs would be an absolute knockout.”

**K-115.** One of the ROCK inhibitors in development is K-115, from the Japanese company Kowa. In a phase 2 randomized dose-response study, 210 patients with primary open-angle glaucoma and ocular hyper-
pertension were divided into four groups. Each group received one of three dosing levels of K-115 or placebo, twice daily for eight weeks. The optimal dose lowered pressure by 3.1 mmHg eight hours after instillation. In comparison, the clinical results documented in the prescribing information for prostaglandin analogues range from 6 to 8 mmHg IOP reduction.

Conjunctival hyperemia, the most commonly reported adverse effect of ROCK inhibitors, occurred in 32 of 49 patients (65.3 percent) who took K-115 0.4 percent, which was determined to be the optimal dose. This drug has now advanced to phase 3 trials. The company anticipates that the drug will be used as monotherapy and will also have additive effects with other clinically available agents, such as prostaglandin analogues and beta-blockers.

More ROCKs in the pipeline. Several other Rho kinase inhibitors are now in earlier stages of clinical testing.

- AR-12286. Aerie Pharmaceuticals is developing a selective ROCK inhibitor to work alone and as part of a fixed-dose combination with travoprost for second-line therapy. In October 2012, results of a phase 2a study evaluating a fixed combination of AR-12286 and travoprost were released. Patients treated with the higher of two dose levels of the combination product demonstrated a statistically significant greater IOP reduction compared with travoprost monotherapy. And the IOP reduction was maintained throughout the day with once-daily evening dosing of the AR-12286–travoprost combination. No serious adverse effects were reported, though transient mild to moderate hyperemia was observed in a minority of patients.

- AR-13324. In November 2012, Aerie reported that it is moving AR-13324 into a phase 2b study. This molecule has a dual mechanism of action to lower IOP: enhancing fluid outflow through the trabecular pathway and decreasing fluid inflow to the eye.

- AMO0076. In September 2012, a Belgian company, Amakem Therapeutics, announced the start of a proof-of-concept phase 2a trial to test the ROCK inhibitor in 80 patients in the United States. The topical drop acts on the trabecular meshwork, where it relaxes smooth muscle to open the outflow channels. It is designed to convert rapidly to inactive form to prevent off-target activity and reduce hyperemia.

Adenosine Receptor Agonists

Like ROCK inhibitors, these molecules work on the trabecular meshwork, but much less is known about them. “There is not as much literature on the mechanism of this class of drugs as there is with ROCK inhibitors,” Dr. Rhee said. He added that adenosine agonists are thought to enhance extracellular matrix turnover in the trabecular meshwork.

Although these agents have been investigated in vitro and in animal research, Dr. Novack said that, to his knowledge, there are no published studies reporting the effect of these molecules in humans.

Trabodenoson. One of the agents now in human trials is trabodenoson, formerly designated INO-8875. Inotek Pharmaceuticals completed the phase 2 multidose investigation of this highly selective adenosine-1 agonist in January 2012. The drug appears to work primarily by increasing the outflow of aqueous via the trabecular meshwork pathway.

In the phase 1/2 trial, trabodenoson, which is administered topically to the eye, was well tolerated and resulted in statistically significant reduction in IOP.

New Drugs: Ho-hum or Home Run? The mantra is that for every 1 mmHg reduction in pressure, there’s about a 10 percent reduction in risk for progression of glaucomatous disease over about five years, Dr. Kaufman said. By that standard, he said a new drug that has a 1-mmHg effect when added to a prostaglandin analogue is “ho-hum,” while a drug that reduces pressure by 3 to 4 more...
mmHg when added to a once-daily prostaglandin would be a home run. What about a 2-mmHg improvement when added to a PGA? That, he said, will probably get you through the FDA to the marketplace for adjunctive therapy, but “it won’t replace the prostaglandins as a first-line therapy.”

**Stand-alone or add-on.** “If you view prostaglandins as the first go-to drugs, and you want another compound to be the first go-to drug, then it’s going to have to be better than the prostaglandins head to head. Better. Or cheaper. Something that gives it an advantage,” said Dr. Kaufman. “But the fact is, most patients are not controlled on one drug, prostaglandin or otherwise. To be successful and become part of our management, it has to be additive to a significant degree.”

We don’t know if we’ll find something significantly additive, something that works on the trabecular meshwork, or on a tissue not yet targeted, and whether that might be more effective, Dr. Kaufman said. But there’s room in the armamentarium for a new class of drugs—even if it’s not a home run. A new class of compounds can be additive to something already effective, he said.

“We don’t know how effective these things will be in addition to prostaglandins. Whatever emerges, it’s not likely to be a true game-changer like the antiretroviral drugs were for AIDS. Those come along once in a lifetime,” he said. “I don’t think the things we’re talking about are remotely in that category.”

**Fundamental research, not serendipity.** Yet whatever emerges will likely be the result of the same kind of methodical research that led to the antiretroviral drugs. “A lot of compounds in ophthalmology were discovered purely by accident,” Dr. Rhee said. He recalled how doctors observed the effect on IOP in patients taking timolol to reduce systemic blood pressure. “All of a sudden, every blood pressure–lowering agent was getting looked at. That’s how both beta-blockers and alpha-2 agonists became glaucoma drugs.”

He predicted the next advances will be less serendipitous. “Part of the reason why ROCK inhibitors really exploded is because of basic fundamental research in the trabecular meshwork,” Dr. Rhee said. “ROCK inhibitors came from advances in understanding how we view the trabecular meshwork regulation of IOP, specifically with regard to cellular mechanics.”

For now, it’s a limited success. We’re further ahead on understanding the cell cytoskeleton but just starting to learn what controls the extracellular matrix, Dr. Rhee said. “But as we do, the hope is a new generation of drugs will be born.”

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