

BIOTECHNOLOGY

Altheos Inc.

ROCK-ing glaucoma prevention

Ever-young baby boomers may expect to drive, read, maybe play golf, and otherwise stay active as they age. However, glaucoma is likely to darken the golden years for millions of them. Glaucoma represents a group of eye diseases generally marked by elevated intraocular pressure (IOP), which, if left untreated, can lead to progressive vision loss and eventually blindness. Glaucoma is the second leading cause of blindness – the first among African-Americans – affecting one in 200 people by age 50, and one in ten 80-year-olds. Estimates are that more than four million people in the US have glaucoma – some 120,000 of them now blind. The worldwide incidence of glaucoma is expected to grow by nearly 30% to 80 million cases by 2020. Presently available glaucoma therapies often fail to control IOP, yet no new pharmaceuticals based on novel mechanisms of action have been approved in 15 years. Altheos Inc. intends to begin clinical trials in the coming year for what it hopes will prove to be the best in an emerging class of topical treatments to stave off vision loss from glaucoma.

Given that large market opportunity, according to Altheos' CEO and co-founder Henry Hsu, the South San Francisco startup found an investor syndicate ready to finance the company, despite the otherwise poor climate for new ventures built around early-stage compounds. The company closed on a \$20.5 million Series A round last April, led by Bay City Capital. The cash went to license a series of selective rho kinase (ROCK) inhibitors for treatment of glaucoma, including a lead candidate, now labeled ATS907, and surrounding intellectual property from Japanese pharmaceutical company Asahi Kasei Pharma Corp. (a division of Asahi Kasei Corp.) Hsu says the raise also gives Altheos plenty of runway to complete preclinical development of ATS907 and carry out clinical trials through the end of Phase II. "Our investors recognize there is a strong need for new drugs," he says. "Over time most glaucoma patients end up on two to three drugs and

even then eventually many need surgery. Physicians would like to have new treatments that work by different mechanisms from the current classes."

Like many diseases of aging, glaucoma results from progressive clogging of drainage systems. A normal, healthy, anterior eye chamber produces aqueous humor at a constant rate. That fluid exits the eyeball in a similarly steady flow through the trabecular meshwork, a sieve-like drain that surrounds the iris, and gets discharged from the eye via a chamber called Schlemm's canal. The most widely held view of the causes of glaucoma points to an increasingly fibrotic tightening of the trabecular meshwork that clogs with protein and other debris, slowing fluid drainage together with stiffening of the meshwork cells. Steadily rising pressure from the buildup of aqueous humor is transmitted to the optic nerve at the back of the eye. That compression, along with hindered blood flow, causes the nerve to degenerate, leading to a progressive loss of sight.

Four classes of drugs given as eye-drops several times daily lower IOP either by increasing outflow of aqueous humor from the eye or decreasing its production. Beta blockers, alpha agonists, and carbonic anhydrase inhibitors decrease production of the fluid. The most widely prescribed class, prostaglandin analogs, increases fluid outflow. Most glaucoma patients eventually require a combination of the drugs to treat their disease – often leading to compliance issues – and even with maximum tolerable dosages may need surgery to open new channels to relieve their IOP.

Sales of existing drugs have been increasing. Together, glaucoma pharmaceuticals totaled about \$4 billion annually worldwide last year. The prostaglandin vasodilators, which boost fluid flow through a secondary channel, the uveoscleral pathway, totaled nearly \$2.7 billion in 2008 sales, with Pfizer Inc.'s *Xalatan* (latanoprost) capturing the lion's share of that, at nearly \$1.75 billion. However, Xa-

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Business: Glaucoma drug development

Founded: April 2009

Founders: Henry Hsu M. (Ken) Kengatharan, PhD, President & CSO

Employees: 10

Financing: \$20.5 million

Investors: Bay City Capital; Novo AS; Canaan Partners; Life Science Angels; Atheneos Capital

Board of Directors: Lester Kaplan, PhD, Chairman (formerly Allergan); Rob Hopfner, PhD (Bay City Capital); Peter Bisgaard (Novo AS); Wende Hutton (Canaan Partners)

Scientific Advisors: Robert N. Weinreb, MD (University of California, San Diego); Janet B. Serle, MD (Mount Sinai School of Medicine); Paul L. Kaufman, MD (University of Wisconsin School of Medicine); Richard Lewis, MD (University of California, Davis)

latan's key patent expires in March 2011, and once it goes generic, the bar will rise for any competitor to prove superior efficacy and safety to gain reimbursement. Hsu thinks his ROCK-inhibitor program should prove to be not only at least as efficacious and safe as latanoprost, but also offer the opportunity for additivity in combination to enhance efficacy.

He learned about the ROCK-inhibitor program at Asahi Kasei through an earlier stint as VP, clinical research at CoTherix Inc., a cardiovascular disease company acquired for \$420 million by Actelion Pharmaceuticals Ltd. in 2007. Asahi Kasei had developed fasudil, the only approved (in Japan) intravenous ROCK inhibitor, for treating subarachnoid hemorrhage. At the time, Asahi Kasei was developing the nascent glaucoma program. While Hsu was still at CoTherix, the company licensed clinical development and marketing rights to fasudil for pulmonary arterial hypertension outside Asia.

ROCK inhibitors like fasudil act as vasodilators and also have anti-inflammatory properties and potentially neuropro-

fective benefits as well. According to Hsu, Asahi Kasei recognized their potential in glaucoma based upon emerging science and screened multiple ROCK-inhibitor compounds. The firm's investigators identified a lead specifically for topical administration in glaucoma. The company made a strategic decision to spin off the glaucoma program several years later and, Hsu says, "considered several options, but liked that we'd be fully focused on moving their program forward and that we have the technical expertise and financial backing to carry it out."

Altheos is behind several companies that have ROCK-inhibitor programs already in clinical trials for glaucoma. Among them are programs from Aerie Pharmaceuticals Inc. and Santen Pharmaceutical Co. Ltd. However, Hsu believes that Asahi Kasei's approach to drug discovery and medicinal chemistry makes the Altheos drug likely to emerge as a fast-follower able to prove itself the best among the new class of drugs. Like the prostaglandins, most ROCK inhibitors' vasodilatation properties can cause redness in the eye. "How do you reduce the redness and other potential adverse events

without losing the compound's effectiveness?" asks Hsu.

The Japanese firm focused on screening for compounds that demonstrated excellent in vivo potency, and then further screened for properties that make them amenable to formulation for topical delivery. As a result, they selected compounds that showed high cellular permeability and, only after entering the anterior chamber, converted to more potent and active metabolites. Once there, ROCK inhibitors relax the hyper-contracted cells of the trabecular meshwork, allowing for increasing outflow through the healthy eye's primary drainage channel and reducing IOP.

As part of the company's initial financing, Lester Kaplan, a member of Bay City Capital's scientific advisory board and former president, R&D and board member at Allergan Inc., which has a large glaucoma franchise, became chair of the Altheos board of directors.

According to Hsu, ATS907, now in late preclinical development, should enter the clinic sometime in the first half of 2011. He says early clinical data in glaucoma tend to be predictive for a drug's performance in pivotal studies. "There is a

standard FDA approval pathway for drugs that claim to lower intraocular pressure. We have a great deal of confidence in our ability to advance our product."

Hsu founded Altheos together with M. (Ken) Kengatharan, now its president and CSO. Kengatharan previously co-founded Athenagen Inc. (later re-named CoMentis Inc.), which in 2008 completed a beta-secretase-inhibitor license deal with Astellas Pharma Inc. with an up-front payment of \$100 million and a potential total value of more than \$760 million. He and Hsu worked together at CoMentis from 2005 to 2009. Both men have extensive experience in vascular pharmacology and preclinical and clinical development. They intend to operate the company with a small internal group of experts and don't anticipate much growth beyond the current 10 employees.

Pointing to Aerie's ROCK inhibitor, which should soon disclose its Phase IIb study results, Hsu claims, "We're rooting for them to succeed. That will further validate the class. And we think we have the best-in-class compound."
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— MARC WORTMAN

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