

BIOTECHNOLOGY

Acucela Inc.

Pursuing new targets for treating blinding eye diseases

The admonition to “slow down and get a clearer view of things” may turn out to be just as apt for ophthalmic drug discovery as for life in general. Preclinical and early clinical data generated by **Acucela Inc.** indicate that oral compounds can slow a key aspect of the visual cycle and perhaps, thereby slow or stop vision loss caused by “dry” age-related macular degeneration (AMD).

At present, there are no FDA-approved treatments for dry AMD, a leading cause of vision loss and ultimately, legal blindness, in people 60 years of age and older. In dry AMD, deterioration of light-sensitive cells at the back of the eye is accompanied by accumulation of cellular debris called drusen. The less common but more severe “wet” form of AMD comes about through abnormal growth of blood vessels, also in the macula or center part of the retina at the back of the eye. Both forms of AMD can cause loss of central (vs. peripheral) vision necessary for basic daily tasks such as recognizing people’s faces, reading and driving.

Because everyone who suffers from wet AMD previously had dry AMD, scientists and investors alike are enthused about the potential for early therapeutic intervention in the disease process. At present, the **National Institutes of Health’s National Eye Institute** (NEI) estimates that 1.75 million Americans have AMD, and this figure will likely double to three million by 2020 as the population ages. The NEI also reports, in a study released at the end of 2008, that some seven million more Americans now have drusen. Although these yellow plaques do not themselves cause vision loss, having

drusen puts individuals at increased risk of developing advanced dry AMD.

Given the serious consequences of dry AMD, and its rapidly increasing rate of incidence, it’s no wonder numerous companies are striving to develop drugs that might supersede the high-dose vitamin and antioxidant mixture NEI cites as the current standard of care. Acucela, **Sirion Therapeutics Inc.**, **Othera Pharmaceuticals Inc.**, **MacuCLEAR Inc.** and **Lynkeus BioTech GMBH** are among the start-ups working to develop drugs for dry AMD.

Although competing firms are further ahead with their clinical trials, Ryo Kubota, the founder, president and CEO of Acucela, believes his firm’s oral drug candidate will ultimately prove the best of the lot. Kubota is an internationally well-regarded ophthalmologist who has performed over 1,000 eye surgeries. Early in his career, while performing postdoctoral research at **Keio University** in Japan, he discovered the gene for myocilin, a secreted protein causative for some forms of juvenile and early-onset glaucoma. Kubota continued his research at the **University of Washington** and eventually licensed the rights to his findings, which provide the technological foundation for Acucela.

Acucela’s lead compound, ACU-4429, is a small-molecule inhibitor of an enzyme called RPE65, known to be involved in the buildup of a toxic vitamin A by-product called A2E. Kubota describes A2E, a complex of vitamin A and retinol, as “a Frankenstein version of vitamin A.” Researchers have long recognized A2E as a key component in an agglomeration of chemical by-products

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Business: Developing oral drugs for dry AMD

Founded: April 2002

Founder: Ryo Kubota

Employees: 40

Financing to Date: \$38.4 million

Investors: SBI Holdings Inc.; Biovision Capital; Trans-Science Inc.; Marubeni Group

Board of Directors: Ryo Kubota; Yoshitaka Kitao (SBI Holdings); Peter Kresel

Scientific Advisory Board: Gerald J. Chader, PhD (Doheny Retina Institute, University of Southern California); Krzysztof Palczewski, PhD (Case Western Reserve University); Thomas A. Reh, PhD (University of Washington); Frank Young, MD, PhD (former FDA commissioner)

called lipofuscin, which is sometimes found in cells (particularly in aging cells) and which is difficult for the body to break down. Lipofuscin appears as an intracellular deposit in the cells of the retinal pigment endothelium (RPE).

Kubota explains the fascinating scientific facts that lead him and others to suspect it will be possible to slow progression of dry AMD, or perhaps even prevent it. It happens that the RPE cells where lipofuscin accumulates have a unique function: they maintain the freshness of the eye’s photoreceptor by phagocytosing the outer portion of it, and they do this all the time. “By constantly clipping the ends of the cells in the photoreceptor, the RPE assure that the photoreceptor is all new about every 10 days,” Kubota says. If lipofuscin accumulates, he goes on, that inhibits the phagocytic pathway, leading to

extra-cellular accumulation of undigested material and formation of the plaques known as drusen.

More than 90% of photoreceptor cells are shaped like rods, and these are interspersed with cells shaped like cones. Kubota points out that all useful daytime vision comes from cone cells, whereas rod cells are vital to night vision. Why is there such a sharp differential in the quantities of photoreceptor cells? Wouldn't it make more sense for the body to have more cone cells to support day vision? Kubota says the ratio is an artifact of evolution: almost all mammals are nocturnal and evolved to have better night vision than day vision, hence the far higher count of rod cells.

Humans' need for dominant cone-cell function is relatively new in the history of evolution—and that's a factor Acucela intends to exploit. The aim of ACU-4429 is "to turn off most of the rod cells' function, because they're not being utilized much anyway in a well-illuminated urban world," Kubota says. "By preserving the rods, we hope to save the cone cells."

There is a key rate-limiting step in the visual cycle, Kubota says, explaining that it comes about when the isomerase RPE65 converts the all-trans forms of retinol, or vitamin A, to 11-cis-retinal. This 11-cis-retinal is then converted into all-trans-retinal upon photon exposure, which is the initial step in sensing light. Prolonged light exposure can lead to an excess amount of all-trans-retinal, and thus to the formation and build up of A2E, Kubota says. He believes it will prove clinically valuable to limit the availability of 11-cis-retinal that can be converted to highly reactive all-trans-retinal. Acucela aims to do that by inhibiting the isomerase RPE65.

Researchers began musing about the therapeutic potential of slowing the visual cycle by interfering with the synthesis of the 11-cis form of vitamin A as far back as the late 1980s, upon learning that the anti-acne drug isotretinoin (*Accutane*) had that property as an unintended side effect. Patients had reported trouble with night vision. While Sirion Therapeutics aims to treat AMD by systemically reducing vitamin A with a retinoid compound, Kubota notes that retinoic acid drugs are known to have multiple undesirable side effects and as such "may not be considered as clinically relevant candidates for the long-term treatment of macular degeneration."

Any compounds that function through this vitamin A-linked mechanism of action will by definition result in reduced night vision, and likely even difficulty seeing in dim light and shadows, but Kubota figures most people facing the alternative of blindness will accept that trade-off. He believes ACU-4429 will prove to be a good drug, in part because it was created through rational drug design to precisely bind to its enzymatic target RPE65 but even more so because that isomerase complex containing RPE65 is expressed only in the eye. "No place else in the body uses 11-cis-retinal as a co-factor," Kubota declares.

Structurally the enzyme RPE65 is unique, he says, and consequently the compound designed to fit it is also distinctive. "We've got a new target, a new mechanism of action, and a new concept for treating blinding eye disease," Kubota points out. At the time he founded Acucela in 2002, venture capitalists looking to reduce risks were not interested in so much novelty; they strongly favored "validated" targets and re-purposed molecules.

"People doubted that an oral compound could even get into the eye, or that deliberately slowing down a major biological process would create disturbances," he recalls. Nevertheless, Acucela has managed to raise more than \$38 million since its inception.

Kubota says he knew enough about the science to commit to creating this enzyme inhibitor. By September 2008, Acucela had enough data to attract a big and beneficent partner: **Otsuka Pharmaceutical Co. Ltd.** agreed to co-develop ACU-4429, making a \$5 million up-front payment, committing up to \$258 million in milestones and financing for clinical trials through Phase II. If the data are good enough to support a Phase III trial, the companies will share the costs, with Otsuka providing a loan facility so that Acucela can cover its share.

The deal with Otsuka also brought Acucela access to a Phase III compound, rebamipide, for treatment of dry eye, a different and far milder disorder than dry AMD. Otsuka will pay all expenses relating to the final clinical development, and even pay Acucela to handle pertinent regulatory matters. If rebamipide wins approval, the partners will negotiate terms for Acucela to co-promote with Otsuka in the US. If all goes well, Acucela will have the means to build a small specialty sales force and pave the way for the launch of ACU-4429. By taking at the outset far more risks than most start-up companies have been able to do in recent years, Acucela has managed to build for itself both promise and stability.

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—DEBORAH ERICKSON