

# Mimetogen Pharmaceuticals Inc.

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**Summary:** Mimetogen Pharmaceuticals Inc.'s founding goal was to use synthetic analogs of nerve growth factor to protect the retinal ganglion cells of the optic nerve that die as glaucoma progresses. In doing so, it intended to show that its drugs provided neuroprotective ability and also enhanced this effect for other treatments prescribed to lower intraocular pressure. Mimetogen validated that program in animals, but given the cost and length of clinical trials for glaucoma, the company switched gears and began developing its NGF mimetics as potential treatments for dry eye.

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## **Mimetogen Pharmaceuticals Inc.**

### **NGF mimetics for ophthalmic diseases**

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Industry Segment: Biotechnology

Business: Small-molecule drugs for ophthalmic disorders

Founded: September 2005

Founders: H. Uri Saragovi, PhD; Garth Cumberlidge

Employees: 4

Financing to Date: Undisclosed

Investors: VIMAC Ventures LLC; iNovia Capital; MSBi Valorisation

Board of Directors: Martin B. Wax, MD (PanOptica); Cédric Bisson, MD (iNovia Capital); R. Dana Ono, PhD (VIMAC Ventures); Garth Cumberlidge; H. Uri Saragovi (McGill University)

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Advances in molecular biology continue shaping the aspirations and business strategies of start-ups across many fields of medicine, as new insights into mechanisms of disease spark ideas for novel treatments. Sometimes, though, ambitions ignited by exciting science have to be refocused as commercial realities become clear.

Such is the case at **Mimetogen Pharmaceuticals Inc.** When the company was founded in 2005, it was intent

on "getting closer to the root problems" of glaucoma than current treatments, which simply reduce intraocular pressure (IOP). Garth Cumberlandidge, a co-founder of the company who continues serving as its president and CEO, explains that Mimetogen set out to protect the retinal ganglion cells of the optic nerve that are known to die as glaucoma progresses. It meant to do so with synthetic analogs of nerve growth factor (NGF) developed by H. Uri Saragovi of **McGill University**, the start-up's other co-founder.

Mimetogen was able to show that its peptide mimetics were, indeed, beneficial in animal models of glaucoma – showing neuroprotective ability on their own, and also enhancing this effect for drugs prescribed to lower IOP. The protection may come about because the compounds, delivered to the vitreous humor through injection, bind to so-called TrkA receptors on retinal ganglion cells. Their presence prevents the death of these neurons.

Although pleased to establish in animals the viability of this novel approach to treating glaucoma, Mimetogen has had to postpone work on its initial goal. The cost and the length of clinical trials necessary to demonstrate proof-of-concept and commercialize a novel drug were deciding factors. Cumberlandidge estimates that Phase II trials alone would take four to five years: "That time line is not appropriate for a venture capital-backed company, so we moved glaucoma down the priority list."

In 2007, the company began looking at NGF mimetics as a potential treatment for dry eye: a condition where efficacy may begin to be seen in a Phase I/II clinical trial after just 28 days, versus the 48 months Mimetogen figured would be necessary to show an impact on the optical nerves of glaucoma patients. Scientific papers published just a year or two earlier in the academic literature helped spur the shift of goal, by linking NGF and BDNF (brain-derived neurotrophic growth factor) with stimulation of mucin production in cultured "goblet" cells from rats. This type of cell, also found in the lung, produces mucin that is important for setting down the foundation of the tear film that covers the cornea and conjunctiva of the eye. This film protects the eye from physical and chemical dangers of the environment, Cumberlandidge explains: "In addition to being a barrier, the matrix that mucin forms has a lubricating function. It is one of the reasons the surface eye is so smooth."

If the proteins themselves were having this effect, Mimetogen figured its NGF mimetics might do the same. So far, so good: testing quickly progressed from cell culture to trials in healthy animals and then on to animal models of dry eye. The data were good enough to support an equity financing in July 2009 (amount undisclosed) and to convince the Food and Drug Administration to approve an Investigational New Drug application in August 2010.

The animal studies involve dosing rats with scopolamine, which dessicates them to the point that they begin showing characteristic signs of dry eye: the amount of their tears is reduced, and the cornea starts to show punctate keratitis. Cumberlandidge says, "We are able to show, by treating for just one day or 14 days with our compounds, then allowing animals to recover from all treatments for seven days an increase in mucin production and a decrease in corneal staining representing keratitis on the cornea." He notes that corneal staining is an FDA-approved endpoint for dry-eye treatment.

Presently, there is just one prescription drug on the market for dry eye – **Allergan Inc.**'s *Restasis*, an ophthalmic formulation of cyclosporine, the immune suppressant that has long helped patients retain transplant organs. The drug generates about \$600 million in annual sales, but Mimetogen thinks it may be able to topple the blockbuster, or at least take significant market share from it. "You have to take it for six months before you see full development of efficacy, and really, only one in about five patients responds," Cumberlandidge declares, adding, "It also burns and stings."

Mimetogen is hoping to generate early evidence that MIM-D3 has the potential to be a better drug than Restasis. Cumberlandidge explains, "Hopefully, it will show efficacy after 28 days, and so far it appears to be extremely comfortable." He says there has been no indication of pain from any of the animals in the company's studies, and toxicology testing shows the compound is very safe.

MIM-D3 is to be formulated as an ophthalmic drop applied topically twice a day. Literally dropping the drug on the conjunctiva keeps systemic exposure very low, though Cumberlandidge notes that NGF is ubiquitous in the body anyway, so adding a little more shouldn't be a problem. The company has observed no ill effects in rats after 28 days of exaggerated dosing with its compounds, and it aims to market drops with concentrations 1,000- to 2,000-fold lower than tested, "so we've got a great safety window," he says.

Although Mimetogen is based in Canada, the company will conduct its Phase II trials in the US. "All the expertise is in the US," Cumberlandidge asserts, explaining that much research on the disease has been accomplished at various Centers of Excellence in the 10 years since Americans identified dry eye as a significant disease. By contrast, in Canada, doctors suggest only that patients buy artificial tears to relieve their discomfort. Restasis is not approved there.

Mimetogen's confidence in MIM-D3 is buoyed in part by studies about nerve growth factor reported in academic literature, and also by the way the compound differs from biological NGF. Cumberlandidge notes that a few years ago, an Italian clinician reported that patients with the most severe form of dry eye, known as neurotrophic keratitis, showed remarkable recovery from the disease after being treated with high-dose NGF from mouse, not the human form. The patients' improvement was of course inspiring, albeit less so because it was accompanied by some ocular pain.

The downside of NGF as a treatment, Cumberlandidge says, is that neuron sprouting causes pain. "Everyone knows this is one of the most difficult factors associated with this protein," he asserts, "so we looked for compounds that would have some of the functions of NGF but not the undesirable ones." He believes MIM-D3 is a promising drug candidate because it mimics one of three so-called beta-turns of the native NGF molecule; these structures on the outside of the molecule are the components that generally react directly with receptors.

Antibody assays spotlighted this particular turn as capable of functioning as an agonist of NGF, whereas other areas of the molecule appear to act as antagonists that block the natural protein's function. Chemical engineering technology developed at McGill University enabled production of a synthetic version of the helpful turn: just three amino acids long, with a total molecular weight of 500 to 600 daltons, Cumberlandidge says this mimetic has a secondary and even a tertiary structure that allows it to work in combination with native NGF, augmenting its effects. "There is usually a good deal of NGF about [in circulation] and MIM-D3 supplements it," Cumberlandidge declares.

Instead of tightly binding to all the receptor sites that NGF does, this compound seems to be a so-called partial agonist that binds only temporarily to the receptor known as TrkA, and not at all to another called p75. If the early data bear out, this trait would be a fortuitous and good one in a drug candidate, Cumberlandidge asserts, because the latter receptor pathway stimulates pro-apoptotic signalling that leads to cell death. So far, he says Mimetogen has been able to stimulate mucin production in the eye's goblet cells by 30 to 50% over the basal rate, "which is much better than 100%," he declares. "If you over-stimulate mucin production, you quickly see down-regulation of the receptors," which means message cannot get through at all.

Adjusting the concentration of MIM-D3 in solution may allow Mimetogen to develop different drug formulations and so treat separate stages of dry eye: a solution with high concentration of the peptide mimetic might be useful for acute treatment, followed by a low dose for maintenance.

If MIM-D3 does show efficacy for treatment of dry eye, then all of the preclinical work done to establish the molecule will be directly transferable to glaucoma and also to retinitis pigmentosa, Cumberlandidge points out. Positive findings might well kindle further interest in Mimetogen's original plan to develop a neuroprotective therapy for glaucoma, and possibly, he suggests, for memory loss caused by loss of neuronal cells. That kind of game-changing potential in a drug candidate might appeal to Big Pharma groups but not, he acknowledges, to venture capitalists seeking speedier development and exits.

For now, Mimetogen intends to develop MIM-D3 through Phase II clinical trials as a treatment for dry eye, and then seek a partner with strong development and marketing capabilities.

The company's investors include VIMAC Ventures LLC, iNovia Capital, and MSBi Valorisation. The amount of financing raised to date remains undisclosed by Mimetogen. – Deborah Erickson