To Protect and Heal


Trefoil Therapeutics was formed on a simple hypothesis: harness the capabilities of fibroblast growth factors (FGFs) to solve a wide range of anterior and posterior corneal diseases.

BASED ON AN INTERVIEW WITH DAVID EVELETH, PHD, AND MARK PACKER, MD

Since its inception in 2013, Trefoil Therapeutics has focused on addressing one particular set of unmet needs in ophthalmology: the treatment of corneal dysfunction affecting the front and back surfaces of the cornea.

Ophthalmic care has recently produced new and novel treatments for myriad ocular conditions—from dry eye, to age-related macular degeneration, to glaucoma, to geographic atrophy. Yet, corneal patients remain remarkably underserved by the current set of clinical interventions. Although some epidemiologic studies suggest that 4% of the population carries a genetic defect of corneal endothelial cells known as Fuchs dystrophy,[1] most of those data are collected in developed nations that have embedded public health services and capacity for screening. Indeed, the global impact of vision loss from conditions affecting the corneal epithelium and endothelium is immense and likely immeasurable.[2]

BUILDING EVIDENCE

To address the unmet need of compromised corneas, Trefoil has maintained a steady focus on one elegantly simple idea: to harness the potential of therapeutic fibroblast growth factors (FGFs) in stimulating faster and more robust healing responses at the cellular level. The company's lead molecule, TTHX1114, currently under development for both epithelial and endothelial indications, is an engineered FGF1 derivative that incorporates unique amino acid sequences to solve the short half-life associated with native FGF1.

"FGFs are some of the most important growth factors in the early development of the cornea," David Eveleth, PhD, Chief Executive Officer, Trefoil, said in a recent interview. "We can demonstrate that they stimulate the growth of endothelial cells under a variety of conditions, but importantly, FGFs also induce a set of genes in these cells that protect the cells against oxidative stress, which is particularly relevant for highly metabolically active corneal endothelial cells. With therapeutic application of FGF1, our molecule offers a protective effect and a proliferative effect that helps the cells that are damaged to recover."[3]

Notably, FGF1 is unique among the family of FGFs in that it binds all known FGF receptors (FGFRs). In theory, TTHX1114, in mimicking physiologic functions, should drive the proliferation and regeneration of cells that are affected by a wide range of anterior and posterior corneal conditions. Similar to native FGF1, TTHX1114 would also arrest intracellular processes that result in cell death, such as autophagy, and thus provide protective benefits.

"In cataract surgery, the major driver of the loss of endothelial cells, the damage that is induced, is, in fact, oxidative stress from the free radicals that are generated by the phacoemulsification process itself. And we know that Fuchs' patients are starting off with fewer endothelial cells than normal, but they're also starting off with a set of endothelial cells that are hypersensitive to oxidative stress," Dr. Eveleth said.

Trefoil recently announced the results of several studies confirming TTHX1114's activity at the 2023 ARVO meeting,, the annual conference held to showcase the top echelon of basic science and translational research in visual science. Over the course of a few days, Trefoil presented evidence that (1) TTHX1114 induced the proliferation of endothelial cells, including those from Fuchs; (2) that oxidative stress induces endothelial cell death and ferroptosis markers, both of which can be prevented by TTHX1114 thus protecting endothelial cells from oxidative-stress-induced death; and (3) that TTHX1114 upregulates wound healing and migration.[4-6]

"Fundamentally, what we demonstrated at ARVO was that our molecule induces proliferative and anti-apoptotic genes that are protective and regenerative for corneal endothelial cells," Dr. Eveleth said.

But Trefoil's run of recent success is perhaps unsurprising, given that the people leading the company are those who were instrumental in unlocking the current understanding of FGFs in the first place. In early 1977, Kenneth Thomas, PhD, a Trefoil co-founder and current consultant, was a post-doc in the laboratory of Ralph Bradshaw, PhD (another Trefoil co-founder and current chair of the scientific advisory board), when he directed the experiments that led to the isolation and identification of acidic FGF, later renamed FGF1. Notably, the two other Trefoil co-founders, Michael Blaber, PhD, a professor of Biomedical Sciences in the College of Medicine at Florida State University, and Dr. Eveleth, were also at one time or another researchers in the Bradshaw laboratory. The team has since surrounded itself with advisors who are equally knowledgeable in FGF science and have been instrumental in formulating its applications.

"Forming Trefoil was sort of like getting the band back together to look at FGF1," Dr. Eveleth said, "but the critical issue that really brought us together was the unmet need, which is that there are a lot of people who have poor vision due to corneal problems, and we can fix that."

FROM BASIC SCIENCE TO FIRST-IN-HUMAN TRIALS

One additional study readout at ARVO 2023—results from the Phase 2 STORM

open-label, 4-arm, dose-controlled/dose-escalation trial of TTHX1114 in eyes with Fuchs dystrophy undergoing Descemet stripping only (DSO) with or without concomitant cataract surgery—builds on the preclinical data of TTHX1114 in showing that Trefoil's central hypothesis is not just theoretical, but also operates in patients in the real world.

DSO is typically associated with a modest degree of success in eyes with Fuchs dystrophy, although visual recovery is often slow and may be incomplete. Furthermore, the oxidative insult inherent to phacoemulsification has the potential to thwart healing responses, thus further perpetuating deleterious effects on postoperative vision. The STORM readout, however, showed that TTHX1114 accelerated the recovery of vision and the resolution of edema. Treated eyes in the high-dose group achieved good vision post-DSO results that were comparable to historical benchmarks associated with corneal endothelial transplantation (DMEK), and faster than other treatment groups or control eyes.

More telling, perhaps, for the proposed mechanism of TTHX1114 is that its benefits were maintained despite cataract surgery: TTHX1114-treated eyes that underwent DSO consistently demonstrated reduced postoperative edema and better vision up to at least 84 days regardless of the added insult of phacoemulsification (induced oxidative stress) suggesting that the drug protected the endothelial cells from that damage.

Trefoil is optimistic that TTHX1114 may provide a solution for eyes with Fuchs disease, considered a common entity, the late-onset form of which affects about 4% of the US population over the age of 40, but which is associated with a 69% risk of ultimately requiring a corneal graft after cataract surgery due to decompensation. A mechanism to improve the environment for postoperative healing would also be applicable after removing dense cataracts and for individuals with diabetes who are also at risk (or "at lower but significant" risk) for prolonged corneal edema following phacoemulsification.

While transient edema does not happen in every patient undergoing cataract surgery, the question remains: if an agent demonstrates benefits in specialized populations—if it promotes healing in eyes at risk for endothelial decompensation—then it could be used to treat any form of edema to ensure every patient has the optimal opportunity to achieve the vision that is expected from a healthy cornea.

"We all know that the cornea is 70% of the refracting power of the eye. The lens is the rest. When we do cataract surgery, we are replacing the lens with something that is as near as perfect as we can achieve, but if the cornea is compromised, there is no benefit to that operation," said Mark Packer, MD, Chief Medical Officer, Trefoil. "By protecting the cornea from the insult of cataract surgery, we really would be making possible the benefits that we intend through replacement of the lens."

ONE PLATFORM, TWO APPLICATIONS

Trefoil's therapy for corneal endothelial dysfunction is an intracameral injection for the treatment of edema related to cornea endothelial dystrophy or damage. Although ultimately restorative for vision, cataract surgery is inherently an insult to the endothelium.

"There is about a 10% to 12% mean loss of endothelial cells, even in perfect phacoemulsification," Dr. Packer said. "But that is really an average. The reality is that some people lose over 50% of their corneal endothelium during cataract surgery. The cornea may be swollen on day 1, and many of them will recover in a few weeks, but then they think they're fine. But what's going on in the background is they're still losing endothelial cells at an accelerated rate after cataract surgery. And then, 5 to 10 years later, many of those people end up with a transplant."

Whether TTHX1114 might be a potential bulwark to endothelial cell loss will start to be answered with its next phase 2 trial, which is expected to enroll patients with persistent edema from surgery and other causes. The application of a synthetic FGF1 in therapeutic applications is not limited to the back of the corneal surface, however. The primary functions of FGFs, participating in cell proliferation; differentiation; migration; and protection, have broad implications for virtually all cells of the human body. Within the context of the cornea, the range of epithelial defects, because they are fundamentally disorders or disorganized healing, are an additional target Trefoil is pursuing with its core technology.

Trefoil's compelling hypothesis received a measurable degree of validation when the company was contacted by representatives of the Department of Defense interested in studying FGFs in the setting of mustard gas exposure. A resulting animal study definitively proved plausibility and set in motion further investigation into the various implications of affecting local FGF activity.[7]

Using a topical (eye drop) formulation, Trefoil has conducted a phase 1 study based on preclinical work supporting efficacy in models of chemical injury and in herpetic keratopathy.[8] The next epithelial clinical study will be a phase 2 study in patients with ocular manifestations of Sjögren's Syndrome, an autoimmune disorder associated with very severe dry eye for which this is no current effective treatment option.

The current armamentarium to speed or aid healing—bandage contact lenses, membranes, and lubricants—are not completely effective.

"We've demonstrated in preclinical models that this molecule can reduce the severity of herpetic keratopathy, and we have high hopes that it will reduce the severity of neurotrophic keratitis and Sjögren's syndrome, and basically any epithelial defect that has an underlying inflammatory component, because the molecule is itself immunomodulatory when given as a topical eye drop on the cornea," Dr. Eveleth said. ■

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