Trefoil Therapeutics
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Restoring vision loss with a regenerative therapy

One molecule, two products; how Trefoil Therapeutics engineered FGF1 (TTHX1114) to enable the treatment of multiple diseases affecting the cornea.

The cornea accounts for 70% of the refractive power of the visual system. However, there are few options for treating patients with significant corneal disease and it remains an area of need. Approximately 4% of people aged 40 years and older have corneal endothelial disease/dystrophy (CED) affecting the back of the cornea, and corneal transplantation is the only treatment option for people with late-stage/severe CED. Patients urgently need an alternative to restore their vision without being exposed to the risks and complications of cornea transplantation, which requires lifelong immunosuppressive therapy. Trefoil Therapeutics has responded by developing TTHX1114, a novel, regenerative product, now in proof-of-concept clinical trials.

A major therapeutic and commercial opportunity awaits TTHX1114 in age-related corneal diseases. In the US and Europe, approximately 600,000 people have Fuchs dystrophy, the most common type of CED, and approximately 200,000 of those have late-stage disease that requires treatment with a corneal transplant within 24 months. Some patients are also diagnosed with CED when being examined prior to cataract or glaucoma implant surgery. Left untreated, patients are at risk of complications following their surgery that could potentially compromise vision recovery.

The number of people diagnosed with CED is rapidly increasing as this is a condition that generally manifests in the fourth or fifth decade of life. The paucity of treatment options means there is limited incentive for early diagnosis. The availability of effective early treatments with more widespread screening programs would enable earlier treatment of CED and eliminate/delay the need for corneal transplants for many people.

Today, the lack of an effective prophylactic treatment for early-stage CED renders physicians powerless when the condition is diagnosed prior to significant vision loss. For those individuals diagnosed with more advanced/late-stage disease, the only option is to wait until a corneal transplant is needed.

The challenging nature of CED makes treatment options limited. Endothelial cell populations decline in every person over time. Most people retain a sufficient number of endothelial cells to retain normal vision throughout their lives, but people with CED suffer more rapid decreases in vision or cell loss. Unless detected prior to a surgical procedure, endothelial changes are typically only diagnosed after several years of slowly worsening vision. A regenerative treatment is needed to reverse age-related loss of corneal endothelial cells (CEC).

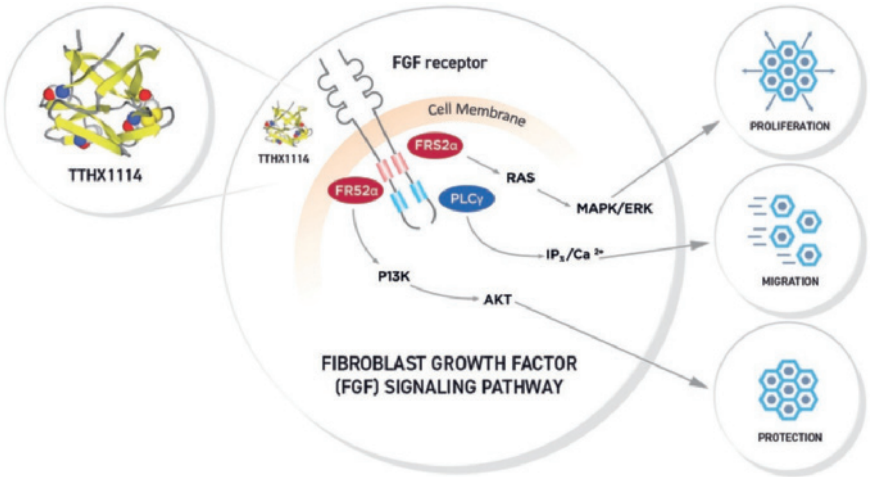

Fig. 1 | Fibroblast growth factor signaling pathway.

A significant opportunity awaits the company that delivers an effective treatment. Corneal transplants cost approximately $20,000 and are associated with longer-term potential spending on steroid therapy and side-effects. Approximately 30,000 corneal transplants are performed annually in the US by approximately 2,500 specialists, for the treatment of patients with significant endothelial disease. In some countries, limited availability of donor tissue means that many patients cannot get transplants.

> **A major therapeutic and commercial opportunity awaits TTHX1114 in age-related corneal diseases**

The data suggest a significant potential for a drug that treats CED without the need for the transplantation of human cornea tissue. Such a therapeutic could also generate use in patients who are diagnosed with corneal endothelial conditions during evaluation for ocular surgery. Restoring the cornea to a healthy state prior to surgery may improve outcomes. Recognising these needs, Trefoil is working to deliver a pharmacological therapy that is effective for many patients diagnosed with corneal diseases.

Engineering a better growth factor

Ralph Bradshaw, David Eveleth, Ken Thomas, and Michael Blaber founded Trefoil in 2013 to further their pioneering work on fibroblast growth factors (FGFs). Bradshaw and Thomas first identified acidic FGF (FGF1) and Bradshaw and the other co-founders, all of whom were his postdocs or doctoral students, continued to advance the field.

The technology underlying Trefoil's engineered FGF1, TTHX1114, builds on the well-known activities of native FGF1 to enable its use as a pharmaceutical for corneal diseases. FGF1 is a potent stimulator of cell proliferation and migration, and has cell protective properties, all key attributes for its use in endothelial disease (Fig. 1). The compound uniquely activates all seven forms of FGF receptors, contributing to its potency. Although FGF1's activities are well known, native FGF1 has a short half-life, which renders it unsuitable as a pharmaceutical agent.

Researchers at the Blaber Laboratory at Florida State University, developed an engineered form of FGF1 (eFGF1), which overcame the pharmacologic limitations of the naturally occurring (native) FGF1, thereby unlocking its therapeutic potential.

Other groups advanced FGF1 as well as different FGFs into human trials before Trefoil. A different FGF1 drug candidate advanced to phase 2 studies for dermal wound healing, and another FGF2 ocular product is approved in Asia. Earlier R&D work, coupled with successful development of other growth factors such as FGF7, shows FGF1 has a well-understood safety profile and has resulted in an established and low-risk method for making the growth factor under GMP conditions.

Other FGF1 programs failed to deliver an approved treatment due to the poor drug-like properties of the molecule. Specifically, FGF1 has low intrinsic thermostability and is prone to unfolding and aggregation, causing it to rapidly lose functional activity. Some groups have used

heparin to stabilize the FGF1, but that negatively affects the cost, manufacturing, safety and efficacy of the drug candidate.

The Blaber Laboratory at FSU overcame the limitations of native FGF1 by engineering it to have improved stability, significantly extending its half-life. After testing a number of FGF1 variants, TTHX1114, which has significantly greater potency than the native FGF1, was selected as a drug candidate. TTHX1114 cannot undergo degradation via cysteine oxidation, unlike native FGF1 and has better pharmacodynamics.

The novel drug candidate (TTHX1114), which is based on innovative engineering, has demonstrated the potential to address the key need in endothelial diseases—replacing lost CECs—by driving the proliferation/regeneration of these cells. The US National Institutes of Health (NIH) recognised the significant potential of the candidate when it accepted TTHX1114 into its Therapeutics for Rare and Neglected Diseases program. Through the program, the NIH funded work to support an Investigational New Drug (IND) application in the US. Trefoil has licensed patents related to TTHX1114 from Florida State University, and extended its intellectual property position with additional company filings.

Validating clinical efficacy

Supported by venture capital funding, Trefoil began studying the effects of intracameral delivery (injection into the anterior chamber of the eye) of its engineered form of FGF1 in patients with CED in 2020. At the time of writing, no patients in the initial clinical trial have experienced drug-related adverse events or dose related toxicities following 88 intracameral injections. TTHX1114 was administered at three dose levels or placebo, all of which appear to be well tolerated. The safety study supported the initiation of a larger, phase 2 proof-of-concept trial in patients with Fuchs dystrophy in 2021.

The phase 2 trial is enrolling Fuchs dystrophy patients who are scheduled to undergo Descemet Stripping Only (DSO), also known as Descemetorhexis Without Endothelial Keratoplasty (DWEK). DSO is a surgical procedure that entails the removal of a small area of the Descemet's membrane (DM). The DM acts as a base for CECs, which attach to its surface. However, in Fuchs dystrophy patients, abnormal collagen deposits, known as guttata, also accumulate on the DM and distort light coming through the cornea. As these guttata disrupt vision, treatment of endothelial disease focuses on removing them.

Historically, surgeons have removed the guttata as part of partial-thickness corneal transplants that replace the removed section of DM with donor material. DSO offers advantages over that older approach, notably because it eliminates the risk of immunologic graft rejection and the need to use long-term topical corticosteroids to ensure the body continues to accept the donor DM. DSO is a simpler and lower-cost surgical procedure than transplantation.

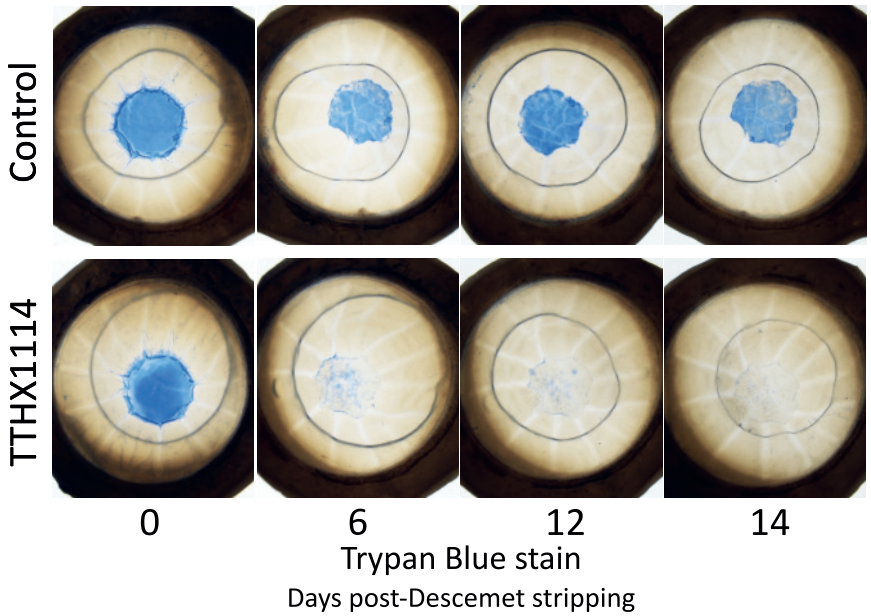

Fig. 2 | Study of TTHX1114. When TTHX1114 was administered to Fuchs dystrophy human corneas immediately following Descemet's stripping, most of the stripped area of the membrane healed within 6 days. In the control arm (Descemet's stripping without TTHX1114), less than 40% of the membrane healed over the course of the ex vivo study.

Without transplant donor material the endothelial cells will only occupy the area stripped of guttata if existing cells migrate from other parts of the cornea. The migration of cells across the cornea after DSO takes months, and in some patients never leads to complete recovery. It is expected that with the addition of TTHX1114 the regeneration of cells will accelerate the recovery process. TTHX1114, which is designed to regenerate CECs, has demonstrated potential to improve and accelerate recovery as shown in figure 2.

> **"The compound uniquely activates all seven forms of FGF receptors, contributing to its potency**

The phase 2 trial is designed to confirm if the regenerative effects of TTHX1114 accelerate the recovery of the stripped part of the DM. Study participants undergoing DSO will receive either zero, one or five injections of TTHX1114. Trefoil will assess the change from baseline in the Best Corrected Visual Acuity, a standard vision test, in each group 28 days after DSO. The analysis will evaluate the effect of TTHX1114 on the speed and magnitude of post-DSO healing, thereby providing a clear indication of efficacy.

Trefoil plans to report data from the phase 2 trial in 2021. If the study is successful, Trefoil will have demonstrated clinical proof-of-concept that its novel, innovative therapy can serve an increasing population of patients who lack other approved or investigational treatment options.

Building an eye disease pipeline

Trefoil is developing the intracameral form of TTHX1114 for endothelial diseases alongside a topical formulation for use in the treatment of conditions affecting the epithelial cells on the front of the cornea. Such epithelial cells regenerate naturally, unlike their endothelial counterparts, but the healing process is painful, lengthy and can result in lifelong vision degradation due to corneal scarring with associated corneal haze. Topical TTHX1114 could reduce pain and minimize the risk of long-term harm by accelerating recovery from corneal ulcers. An IND for the topical formulation of TTHX1114 is expected to be filed in 2022 with clinical trials to begin soon after.

The two-program pipeline uniquely positions Trefoil to address conditions affecting the front and back of the cornea, which lack innovative new products/treatment options. By advancing these two innovative programs, Trefoil stands to provide a better standard of care to improve the vision of millions of people who have limited treatment options today, and encourage their earlier diagnosis and treatment.

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