MeiraGTx
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Taking gene therapy to the next level

MeiraGTx is opening new frontiers in gene therapy by pioneering next-generation gene-regulation platforms to transform the application of gene therapy. The company is developing innovative gene therapy approaches for debilitating eye disorders, xerostomia (dry mouth) syndromes and neurodegenerative diseases such as amyotrophic lateral sclerosis (also known as Lou Gehrig's disease).

MeiraGTx is a clinical-stage gene therapy company based in New York and London that is developing innovative gene therapies to transform the lives of patients suffering from inherited and acquired disorders.

Leveraging advances in adeno-associated virus (AAV)-based gene-delivery, the company is developing novel therapies for radiation-induced xerostomia and severe inherited retinal disorders such as Leber congenital amaurosis (LCA), achromatopsia (ACHM) and retinitis pigmentosa.

The company is also pioneering gene therapies to introduce novel transgenes to treat neurodegenerative diseases—such as amyotrophic lateral sclerosis (ALS), among others—for which there are no disease-modifying treatments.

MeiraGTx is unique in developing a gene-regulation platform that uses orally available small molecules to control the timing and dosage of therapeutic proteins delivered by gene therapy; these developments promise to transform this therapeutic modality.

Reversing morbidity for cancer survivors

Xerostomia—the reduction or absence of saliva—is a debilitating and frequent side effect of radiation treatment for head and neck cancers, and it results in oral infections, mucositis, dysphagia, dental caries and severely diminished quality of life.

MeiraGTx has developed an AAV-based gene therapy that restores salivary flow in surviving salivary duct cells by expression of the water channel aquaporin 1 (AQP1). The company is conducting a phase 1/2 clinical trial of a minimally invasive oral procedure that delivers the human *AQP1* gene to patients with radiation-induced xerostomia. MeiraGTx has orphan drug designation (ODD) from the US Food and Drug Administration for this indication.

A focus on vision

MeiraGTx has several therapies to treat inherited retinal degenerative disorders in collaboration with the University College London Institute of Ophthalmology and Moorfields Eye Hospital.

The most advanced program, in a phase 1/2 clinical trial, is in LCA, a group of autosomal-recessive retinal dystrophies that cause severe sight impairment in childhood; there is currently no treatment for LCA. Up to 16% of cases of LCA have a deficiency in the gene encoding retinoid isomerohydrolase (*RPE65*), which has a key role in the regeneration of visual pigment following exposure to light. MeiraGTx's OPTIRPE65, an engineered AAV, drives expression of *RPE65* to clinically relevant levels.

MeiraGTx pipeline

Program	Product candidate	Indication	Research	Preclinical	Phase 1/2	Status
Clinical	Xerostomia	Xerostomia (*AQP1*)				▪ Phase 1/2 ongoing
	A001	LCA 2 (*RPE65*)				▪ Phase 1/2 ongoing
	A002	ACHM (*CNGB3*)				▪ Phase 1/2 1H 2017
	A003	ACHM (*CNGA3*)				▪ Phase 1/2 1H 2017
	A004	X-linked *RP* (*RPGR*)				▪ Phase 1/2 1H 2017
Preclinical	A005	Dry AMD (rod to cone)				▪ First human trials expected 2018
	A006	Wet AMD (anti-VEGFR2, anti-PDGFRβ)				▪ First human trials expected 2018
	A007	ALS and *FTD* (*UPF1*)				▪ First human trials expected 2018

Figure 1: MeiraGTx is developing a broad pipeline of innovative gene therapies. 1H, first half of the year; ALS, amyotrophic lateral sclerosis; AMD, age-related macular degeneration; *AQP1*, aquaporin 1; *CNGB3*, cyclic-nucleotide-gated channel beta 3; *CNGA3*, cyclic-nucleotide-gated channel alpha 3; FTD, frontotemporal dementia; LCA 2, Leber congenital amaurosis; RP, retinitis pigmentosa; *RPGR*, retinitis pigmentosa GTPase regulator; PDGFRβ, platelet-derived growth factor receptor-β; VEGFR2, vascular endothelial growth factor receptor 2.

Another indication is complete congenital ACHM, an inherited eye disorder characterized by absence of daylight vision, aversion and extreme sensitivity to light, color blindness, and progressive loss of photoreceptor cells. In 50% of patients with ACHM, the disorder is caused by a mutation in the gene encoding cyclic-nucleotide-gated channel beta 3 (*CNGB3*), whereas 25% of patients harbor a mutation in the gene encoding cyclic-nucleotide-gated channel alpha 3 (*CNGA3*).

MeiraGTx has developed two gene therapy products designed to rescue the function and increase the survival of retinal cone cells in ACHM. The first therapy supplements photoreceptor cells with *CNGB3* delivered via an AAV, whereas the second supplements *CNGA3*. Phase 1/2 clinical trials in ACHM caused by these mutations are expected to start next year.

The third program in MeiraGTx's deep ocular pipeline (**Fig. 1**) centers on retinitis pigmentosa, a leading form of blindness that is inherited autosomally or linked to the X chromosome (XLRP). Up to 20% of cases of retinitis pigmentosa—and more than 70% of cases of XLRP—are caused by mutations in the gene encoding retinitis pigmentosa GTPase regulator (*RPGR*). Most patients with this form of retinitis pigmentosa progress from early childhood night blindness, to reduction of their visual field and visual acuity, and then to legal blindness in their fourth decade.

MeiraGTx has developed a gene therapy product to restore *RPGR* function. This therapy is undergoing preclinical evaluation and is scheduled to enter phase 1/2 clinical studies in 2017.

Tackling a killer

Neurodegenerative disease presents an enormous unmet need that gene therapy has the potential to address in a transformative way as targets and mechanisms are elucidated.

MeiraGTx is leading the field through its ALS program, developed in collaboration with researchers at Weill Cornell Medicine and Louisiana State University. The majority of patients with ALS exhibit toxic accumulations of TAR DNA-binding protein 43 (TDP43). MeiraGTx and its collaborators aim to neutralize the toxic effect of this accumulation by boosting nonsense mediated decay (NMD), one of the cell's quality control systems, through the UPF1 protein, its main effector.

The company has a gene therapy in preclinical development that delivers *UPF1* to neurons to boost their NMD pathway and thus reduce or eliminate the toxic effects of TDP43.

Making a control switch

Gene therapies developed to date deliver therapeutic proteins directly to cells where they are expressed continuously. Critical to the future of this therapeutic strategy is the ability to modulate levels of therapeutic proteins—on or off, up or down.

MeiraGTx is developing a suite of genetic switches that allow the expression of a transduced gene to be regulated. The new technology, invented in-house at MeiraGTx, will enable the maintenance of correct levels of a transduced gene in patients simply through oral administration of a small molecule. Precisely dosed gene therapies with the platform are already in development with promising preclinical results.

According to CEO Zandy Forbes, "MeiraGTx is poised to make substantial contributions to the treatment of serious disease with unmet needs through our deep pipeline of AAV-based gene therapy programs. Additionally, we are very excited by our regulation platform, which will globally transform the application of gene therapies."

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