THE EMERGENCE OF LONGEVITY BIOTECHNOLOGY IN EYE CARE


Several strategies are being explored to halt or reverse the effects of aging.

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You may think aging is what happens to an organism as time passes. That is *chronological* aging. *Biological aging*, on the other hand, is loss of the ability of an organism to recover from stressors and to maintain homeostasis.[1,2] Therapies targeting the mechanisms behind biological aging could potentially treat or prevent many conditions such as Alzheimer disease, heart disease, and glaucoma.

Recent research into aging has moved away from merely investigating and slowing the process of aging to exploring strategies with the ability to reverse age-related changes; progress in this area appears to be accelerating rapidly.[3,4] Most of these strategies revolve around addressing the hallmarks of aging.[3,5] Scientists are also developing specific biomarkers of aging, based on lab values and epigenetic aging clocks, to aid in quantifying aging and in slowing or reversing it.[1,6]

Aging is the most common and greatest risk factor for most major diseases, especially those pertaining to the eye. Often, ocular diseases are some of the first targets investigated for new therapies, given the impact of visual impairment on quality of life, the relative safety advantages, and the variety of potential drug delivery options. Many readers may be aware, for instance, of the many genetic therapies being explored for inherited retinal diseases and other ophthalmologic disorders.

Voretigene neparvovec (Luxturna, Spark Therapeutics) was the first such agent, a directly administered genetic therapy, to be approved by the FDA in 2017.[7,8] Lesser known and newer interventions being investigated include epigenetic, senolytic, and mitochondrial therapies, all approaches that target hallmarks of aging.

This article explores the coming evolution in longevity biotechnology

AT A GLANCE

- Therapies targeting the mechanisms behind biological aging could potentially treat or prevent many conditions associated with aging, including some eye diseases.
- In addition to genetic therapies, lesser known interventions being explored include epigenetic, senolytic, and mitochondrial therapies, all targeting the hallmarks of aging.
- Investigations of these therapies range from preclinical to early clinical stages.

and its application to ocular diseases. Specifically, it reviews trending strategies and provides examples of companies pursuing clinical research in each area.

EPIGENETIC TARGETED THERAPIES

The term *epigenetics* refers to heritable but modifiable features of the genome that contribute to gene expression.[9] Essentially, epigenetics can explain how the environment affects the development of an organism. For example, it is known that children born to mothers during periods of famine have increased susceptibility to psychiatric illness and obesity via epigenetic mechanisms.[10,11]

Recently, researchers have found that reprogramming of the epigenome can be used to rejuvenate cells.[12-14] Shinya Yamanaka won a Nobel prize in 2012 for his groundbreaking research published in 2006, in which he and his colleague described the transcription factors Oct4, Sox2, Klf4, and cMyc.[15,16] These transcription factors, now known as *Yamanaka factors*, can cause mature somatic cells to revert into induced pluripotent stem cells (iPSC).

It has recently been shown that these factors can also be used to rejuvenate somatic cells without completely turning them to iPSCs.[12,13] This has been achieved in two ways: by limiting the amount of time cells are exposed to the factors or by using only a partial set of the factors.

This technology has been delivered via an adeno-associated viral (AAV) vector in several mouse models of glaucoma, optic nerve injury, and normal aging.[12] The specific AAV applied, Tet-Off AAV2, uses tetracycline class drugs as on-off switches to induce transcription for a controlled duration. Investigators reported in the December 2020 issue of *Nature*, "Turning Back Time," that this treatment resulted in murine optic nerve axon regeneration and reversed vision loss.[12] This is an unprecedented finding, suggesting that aspects of ocular aging may be reversible, while also giving hope to patients who have experienced vision loss due to glaucoma.

Messenger RNA, or mRNA, technology can also be employed to introduce transcription factors. Turn Biotechnology is investigating the use of mRNA technology for epigenetic reprogramming. The company's proprietary technology, epigenetic reprogramming of age (ERA), restores the youthful functionality of targeted cells while maintaining cell type integrity. Potential targets include ocular surface disease, corneal disease, age-related macular degeneration (AMD), and glaucoma. TRN-004 (Turn Biotechnology) is in the in vivo preclinical stage of investigation for ocular surface disease (Figure 1).[17]

SENOLYTIC THERAPIES

Senolytics are a small class of drugs being investigated for the potential to eliminate senescent cells and improve human health. Although epigenetic therapy appears promising, it may not result in a fully rejuvenated phenotype. The accumulation of senescent cells, a hallmark of aging, results in disorder of tissue structure and function.[18,19] They are also known to secrete senescence-associated secretory phenotype (SASP), which results in inflammation and degradation of the surrounding milieu. Ridding the body of these cells is seen as a potential method of reversing age-related decline.[18]

Researchers at the Mayo Clinic recently reported that clearing senescent cells with senolytics not only slowed aging, but also partially reversed aspects of tissue dysfunction in mice, thereby extending their healthy lifespan.[20]

Unity Biotechnology is investigating the use of senolytics in ocular therapeutics. Investigators have reported that high levels of senescent cells are associated with ophthalmologic disorders such as AMD and diabetic macular edema (DME).[21] In preclinical models of diabetic retinopathy, the senolytic UBX1325 (Unity Biotechnology) has demonstrated improvement in retinal vasculature and function (Figure 2).[21,22] UBX1325 works, reportedly, by inhibiting the molecule Bcl-xL, which is highly expressed in diseased blood vessels during retinopathy and has been shown to engage pathways of cellular senescence.[21,22] UBX1325 reduces abnormal blood vessel growth and improves retinal function and vascular leakage in preclinical models. It restores healthy vascularization and, unlike anti–vascular endothelial growth factor (VEGF) therapies, also improves avascular areas.

Unity recently reported positive findings in its phase 1 trial demonstrating improvements in BCVA and central subfield thickness in a small group of patients previously nonresponsive to anti-VEGF therapy.[23] This seems promising, given that this phase 1 trial was designed to assess safety and dosing and not efficacy.

MITOCHONDRIAL THERAPIES

Mitochondrial therapies are also being investigated for their cellular rejuvenation potential.[24] Because mitochondria are the producers of energy in the cell, they are thought to play a large role in neurologic diseases. In the eye, they are potential targets for treating disorders of the retina and optic nerve.[25,26]

Improving mitochondrial function is essentially the mechanism of photobiomodulation or low-level light therapy.[27] Photobiomodulation is a relatively new modality in eye care; details of its potential uses were described in the July/August issue by Craig Thomas, OD ("Understanding Photobiomodulation Therapy," page 24; bit.ly/0721MODCT).

A multitude of supplements that are thought to support mitochondrial function are also being explored. Popular examples include CoQ-10 and NAD+ boosters. Large human trials have not been undertaken to

Image courtesy of Turn Biotechnology.

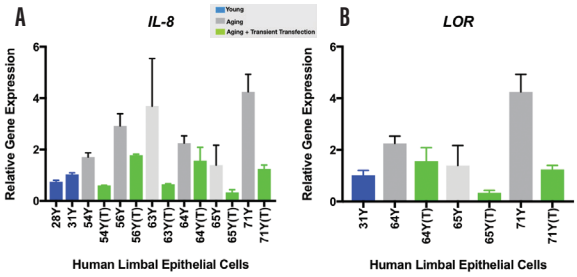

Figure 1. As people age, they begin to express more proinflammatory cytokines, such as interleukin-8 (IL-8), in the limbal epithelial cells of the eyes (A). ERA treatment of these cells from aged subjects reduced the expression of this inflammatory factor to youthful levels (B). Another protein that increases with age in limbal epithelial cells is loricrin (LOR), which is known to degrade the corneal matrix. Treatment of aged cells with ERA restored LOR expression to youthful levels, showing that ERA can prevent excess degradation of the aged eye. Figure reflects research of Albert Y. Wu, MD, PhD.

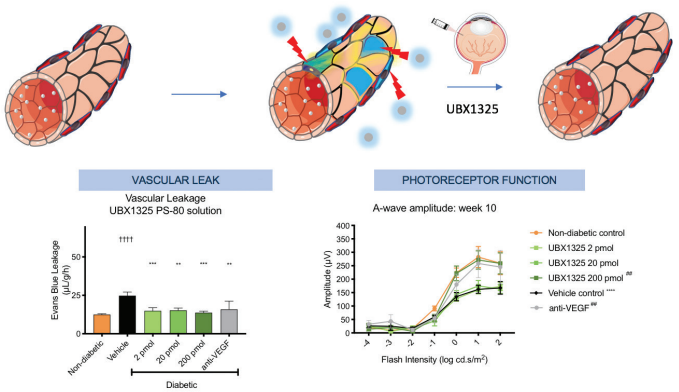

Image courtesy of Unity Biotechnology.

Figure 2. UBX1325 (Unity Biotechnology) reestablished barrier function and improved photoreceptor function in a mouse model of diabetes.

establish benefits of these supplements, and recommendations to patients for mitochondrial support are therefore not yet advisable.[28-30]

A few biotechnology companies are working on mitochondria-based therapies, including at least two in ophthalmology.

MC16 (MitoChem Therapeutics) is in a new class of small molecules designed to protect mitochondrial homeostasis, according to the company. In April, the FDA conferred orphan drug status on MC16 as a potential therapy for retinitis pigmentosa, and secondary indications to be explored include dry AMD and glaucoma.[31,32] According to the company, "MC16's protective mechanism is designed to be disease- or gene mutation-agnostic, with the unique potential to treat all forms of retinitis pigmentosa."

Elamipretide (Stealth Biotherapeutics) is a peptide that reportedly binds to a component in the inner mitochondrial membrane and increases mitochondrial function through a variety of mechanisms. It is currently in phase 2 trials for treatment of AMD and Leber hereditary optic neuropathy.[33]

THE FUTURE LOOKS BRIGHT

A number of emerging technologies with the potential to rejuvenate ocular tissues and reverse age-related decline are being explored in preclinical and clinical investigations. The continued pursuit of these technologies is vital, as they may have the potential to restore vision loss and improve quality of life for many of our patients. ■

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