

27. Gene therapy for long-term decrease of intraocular pressure

(Duke University)

► Asset Overview

Product Type	Gene Therapy
Diseases Area	Other
Indication	Glaucoma
Current Stage	Discovery
Target	miR-146
MoA	<ul style="list-style-type: none"> miR-146a was upregulated in senescent fibroblasts and trabecular meshwork (TM) cells and that its upregulation could act as a brake to excessive production of inflammatory cytokines that are part of the senescence-associated secretory phenotype. The TM is constantly subject to mechanical forces such as IOP spikes, cardiac cycle, blinking, and eye movement.
Brief Description	<ul style="list-style-type: none"> miR-146 affected the expression of genes potentially involved in outflow homeostasis at basal levels and under CMS. Both lentiviral and adenoviral vectors expressing miR-146a resulted in sustained decreases in IOP ranging from 2.6 to 4.4 mmHg. Long term follow-up of rats injected with lentiviral vectors showed a sustained effect on IOP of 4.4 ± 2.9 mmHg that lasted until rats were sacrificed more than 8 months later. Eyes showed no signs of inflammation, loss of visual acuity, or other visible abnormalities.
Intellectual Property	US20220273694A1
Publication	<ul style="list-style-type: none"> Long-Term Decrease of Intraocular Pressure in Rats by Viral Delivery of miR-146a. TVST (2021) MicroRNA-24 Regulates the Processing of Latent TGFβ1 During Cyclic Mechanical Stress in Human Trabecular Meshwork Cells Through Direct Targeting of FURIN. J. Cell Physiol. (2011) Modulation of inflammatory markers by miR-146a during replicative senescence in trabecular meshwork cells. IOVS (2010)
Inventors	Pedro Gonzalez, Coralia C. LUNA

► Highlights

- When subjected to CMS, cells transfected with miR-146 inhibitor showed an average increase in expression of the selected genes of 446% compared with cells transfected with scrambled inhibitor.
- The difference in IOP between the injected and the contralateral (non-injected) control eyes decreased over time with an average difference of 2.61 ± 1.43 mmHg
- Analyses of semi-thin sections of the angle from three rat eyes injected with Lenti-CAGmiR-146a and three non-treated contralateral controls showed no apparent abnormalities or signs of inflammation associated with Lenti-CAG-miR-146a injection and no evident differences with the control eyes

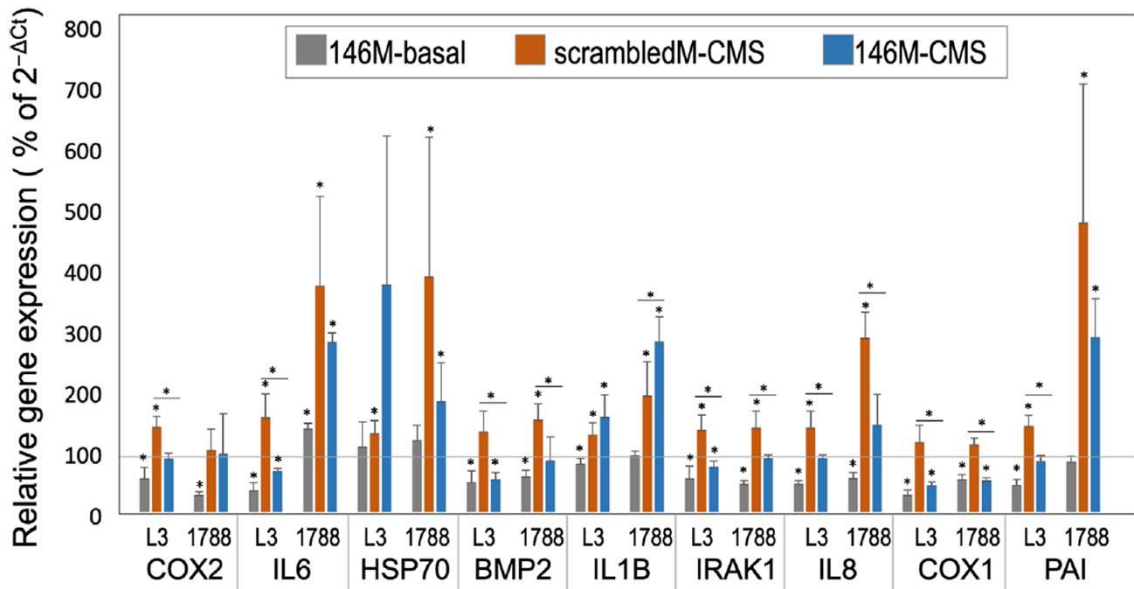
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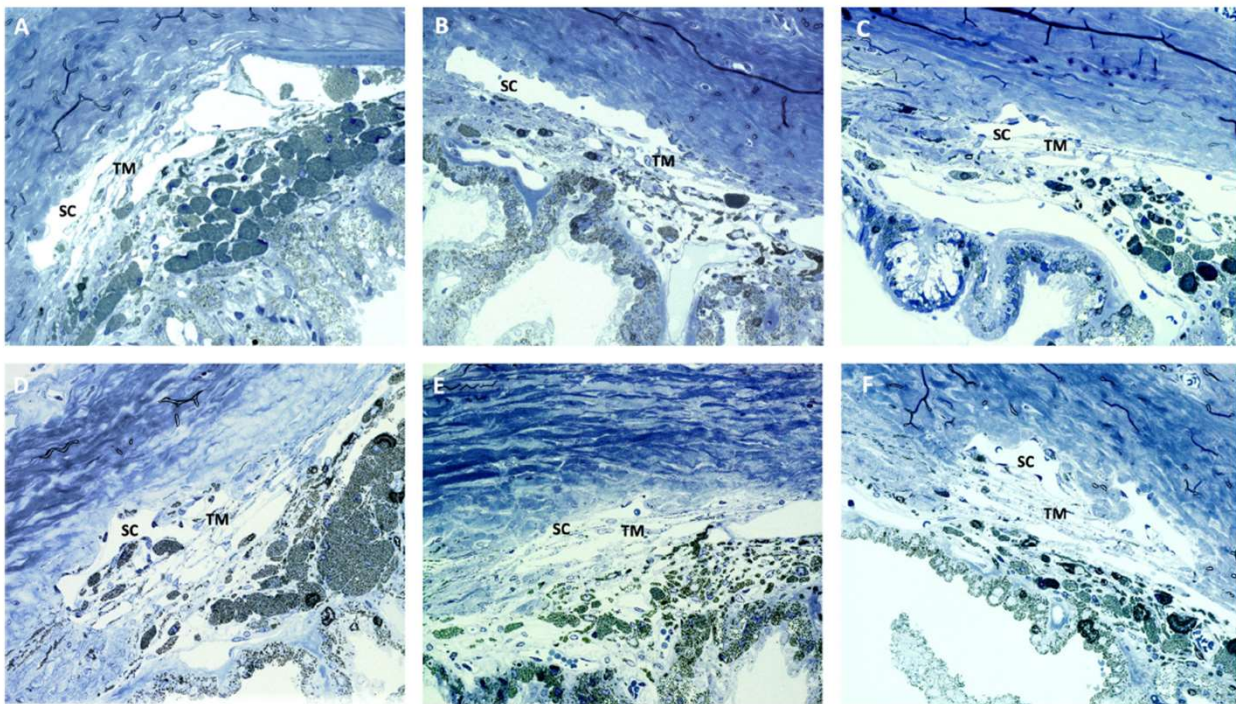
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Key Data

Effects of overexpression of miR-146a on gene expression in HTM cells at the basal level and under CMS



Semi-thin sections of rat eyes angle transduced with Lenti-CAG-miR-146a or contralateral control eyes



[9 months after injection] (A–C) Representative images of Lenti-CAG-miR-146a transduced eyes. (D–F) Representative images of contralateral eyes ($n = 3$). SC, Schlemm's canal; TM, trabecular meshwork.