miRagen

Restoring Biological Harmony for Patients with Debilitating Disease

Restoring miRNAs of the miR-183/96/182 cluster ameliorates symptoms of retinal degeneration in a mouse model of retinitis pigmentosa

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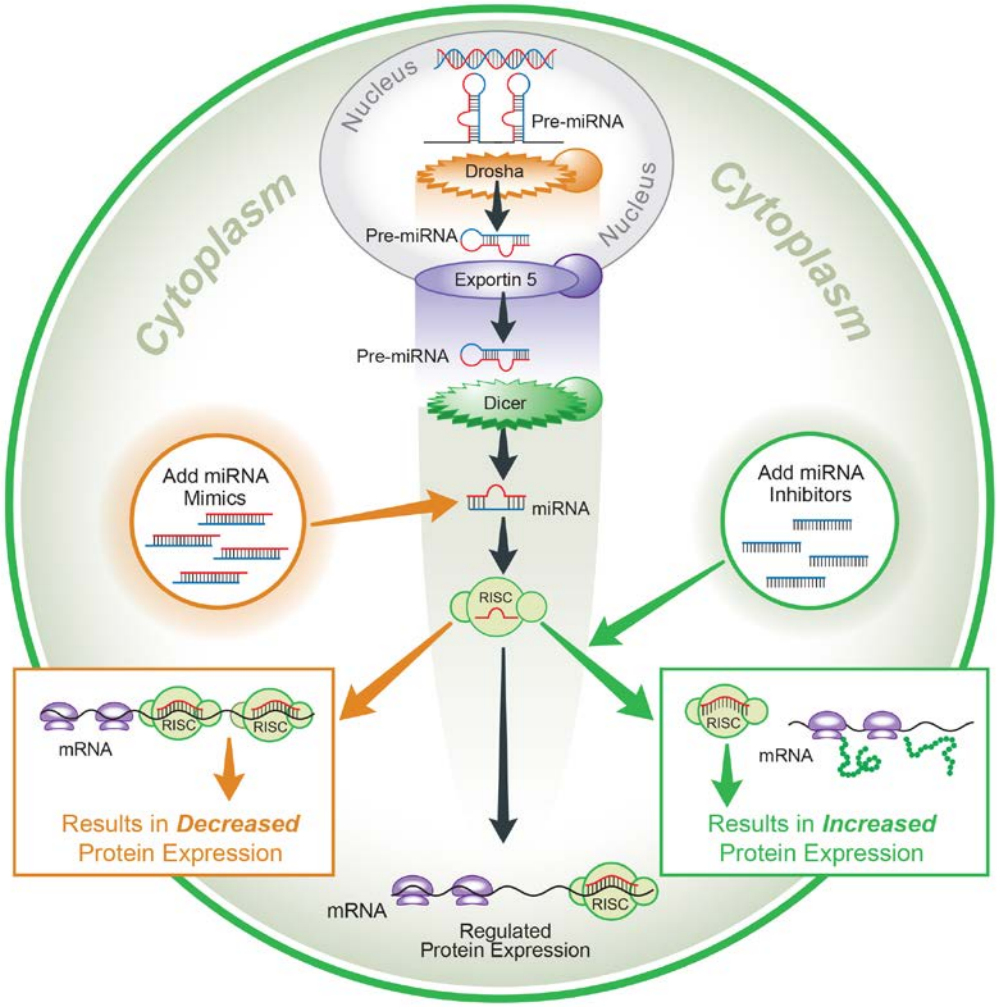
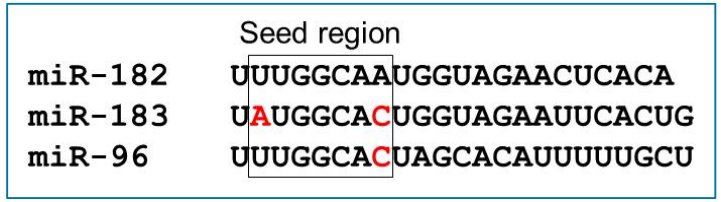
microRNA Therapeutics Regulate Systems Biology to Modify Disease



- microRNA-targeted therapy is focused on disease modification by restoring homeostasis to dysregulated processes
- microRNAs regulate complex biological systems
- microRNA-targeted therapies are intrinsically focused on disease-relevant pathways
- microRNA therapeutics particularly suited for complex, multigenic disorders

miRNA 183/96/182 Cluster

- miR-183/96/182 are related microRNAs expressed from a single transcript
  - sensory organ-specific with high expression in INL/ONL and photoreceptors (rods > cones)



- Predicted targets include genes involved in visual cycle, retinal disease, intracellular signaling, and apoptosis

- Genetic disruption causes loss of sensory organ function
  - Syndromic hearing loss in humans is linked to loss of miR-96
  - Syndromic retinal degeneration in preclinical models
    - **Rd10 model (mouse model of retinitis pigmentosa)**

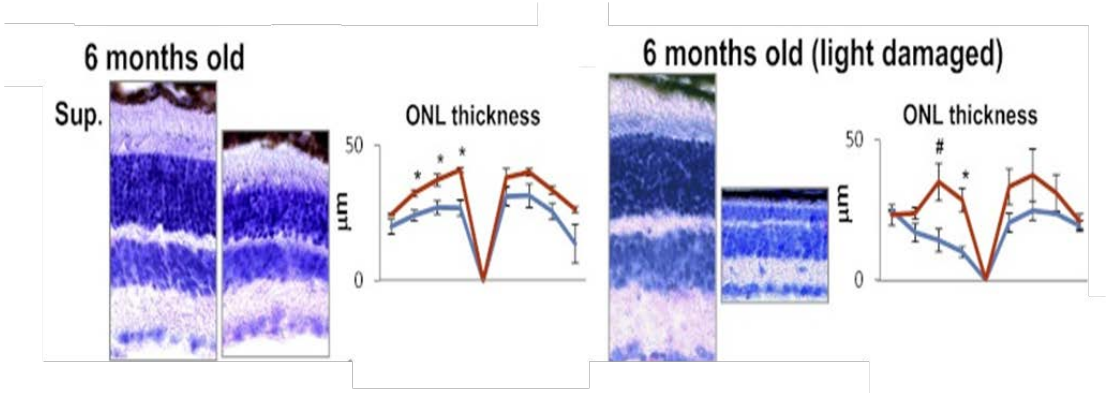
    ↓ miR-183, miR-96, and miR-182 in mouse models of RP

    ↓ miR-183/96/182 function → progressive retinal degeneration

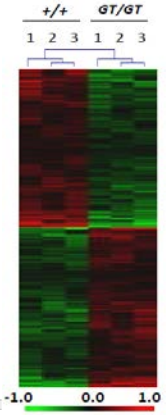
Genetic Modulation of the Cluster Validates these microRNAs in Photoreceptor Function

miR-183/96/182 loss of function

- *Lumayag et al. 2013 PNAS (KO mouse)*
- *Zhu et al. 2011 JBC (Sponge transgenic mouse)*



miR-183/96/182 KO mice have severe loss of photoreceptor layer



Functional annotation:

- **Synaptogenesis**
- **Synaptic contact**
- **Nerve impulse transmission**
- **Phototransduction**
- **Retinal disease genes**

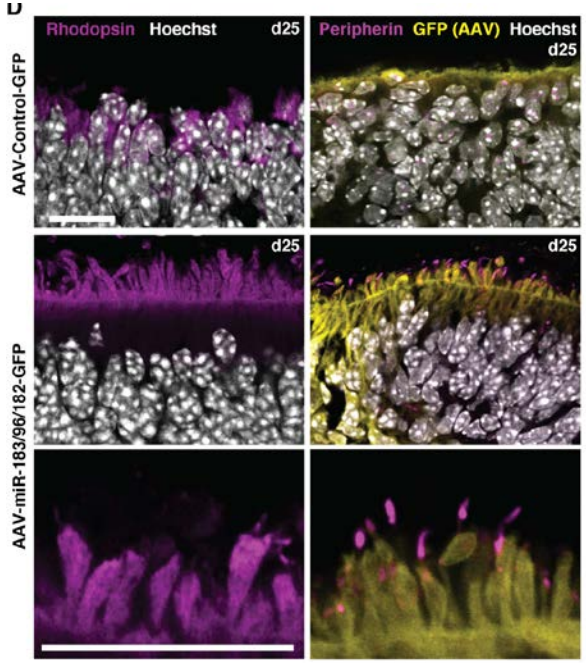
→

↑ Retinal degeneration

↑ Susceptibility to light damage

AAV-mediated expression of miR-183/96/182 in retinal cones

Busskamp et al. 2014 Neuron



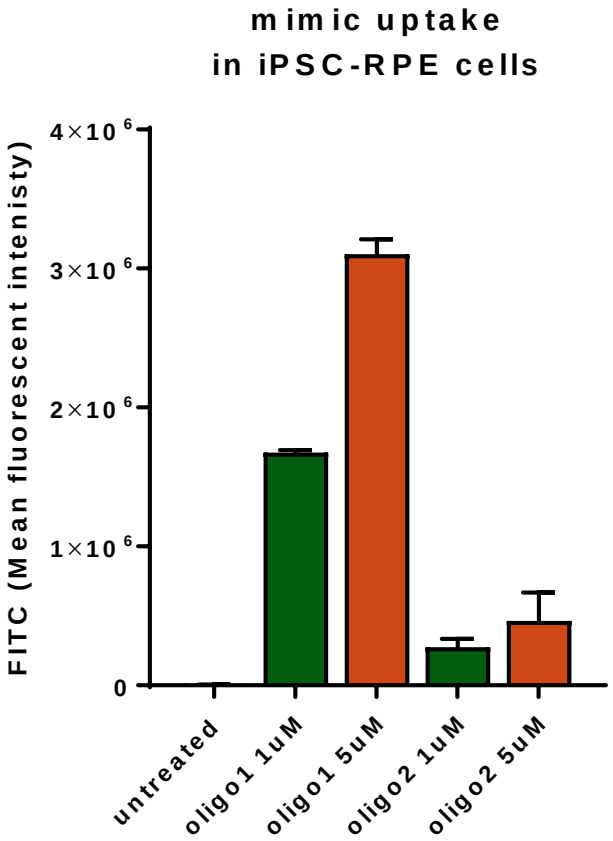
- **miR-182 and miR-183 necessary and sufficient for formation of distal photoreceptor structures (outer segments)**
- **Induced light response**

miRagen has Synthesized Mimics for Each microRNA in the miR-183/96/182 Cluster

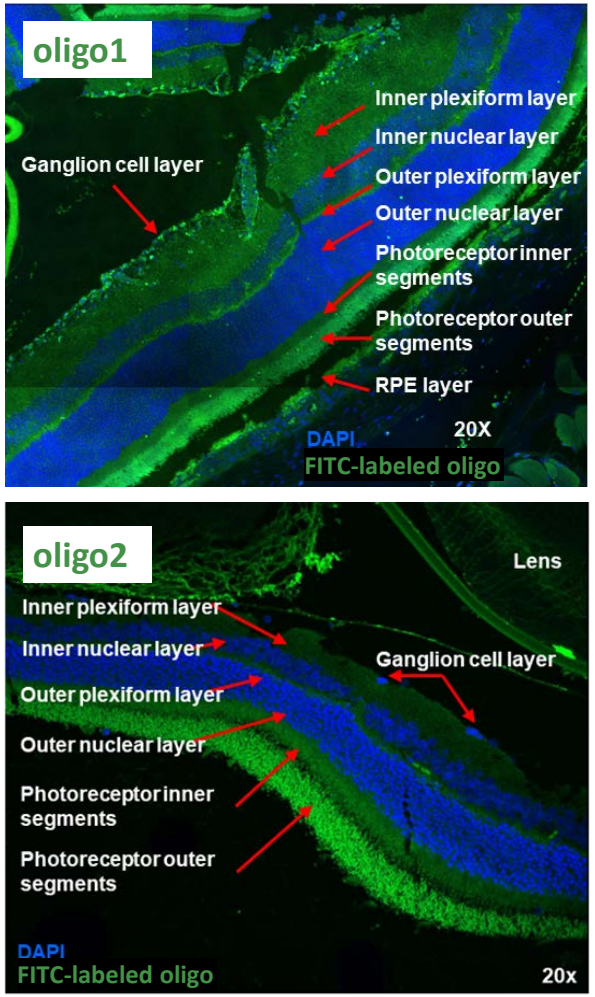
- Mimics are highly soluble
- Mimics of the miR-183 cluster have been assessed in primary retinal cells and in a mouse model of retinal degeneration (retinitis pigmentosa)
- Mimics are well tolerated via intravitreal injection at all dose levels, up to and including the highest deliverable dose
- Mimics can be delivered as individual microRNAs or as a pool of multiple microRNAs

Efficient Oligo Uptake and Sustained Activity in Photoreceptors After Intravitreal Injection

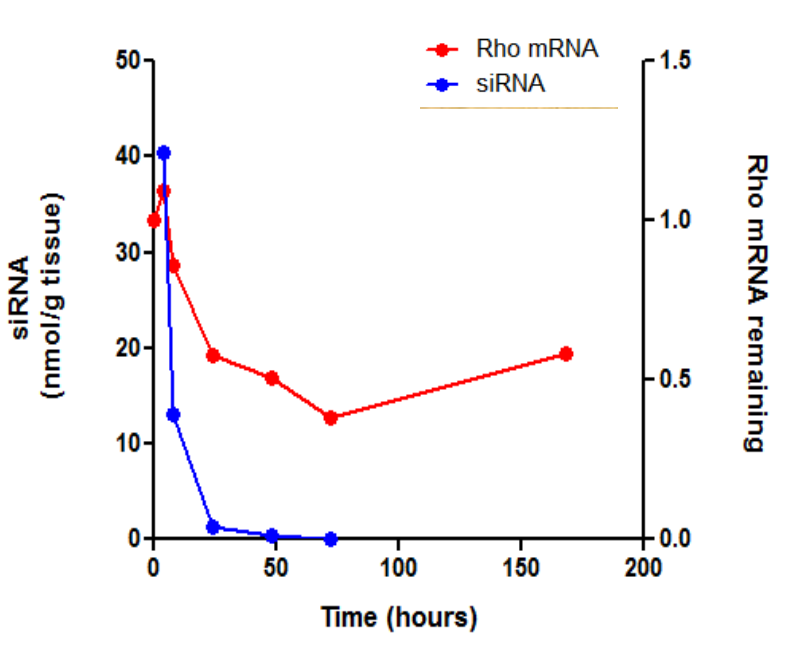
hiPSC-RPE cells, passive uptake



WT rat, single IVT injection



WT mouse, single IVT injection



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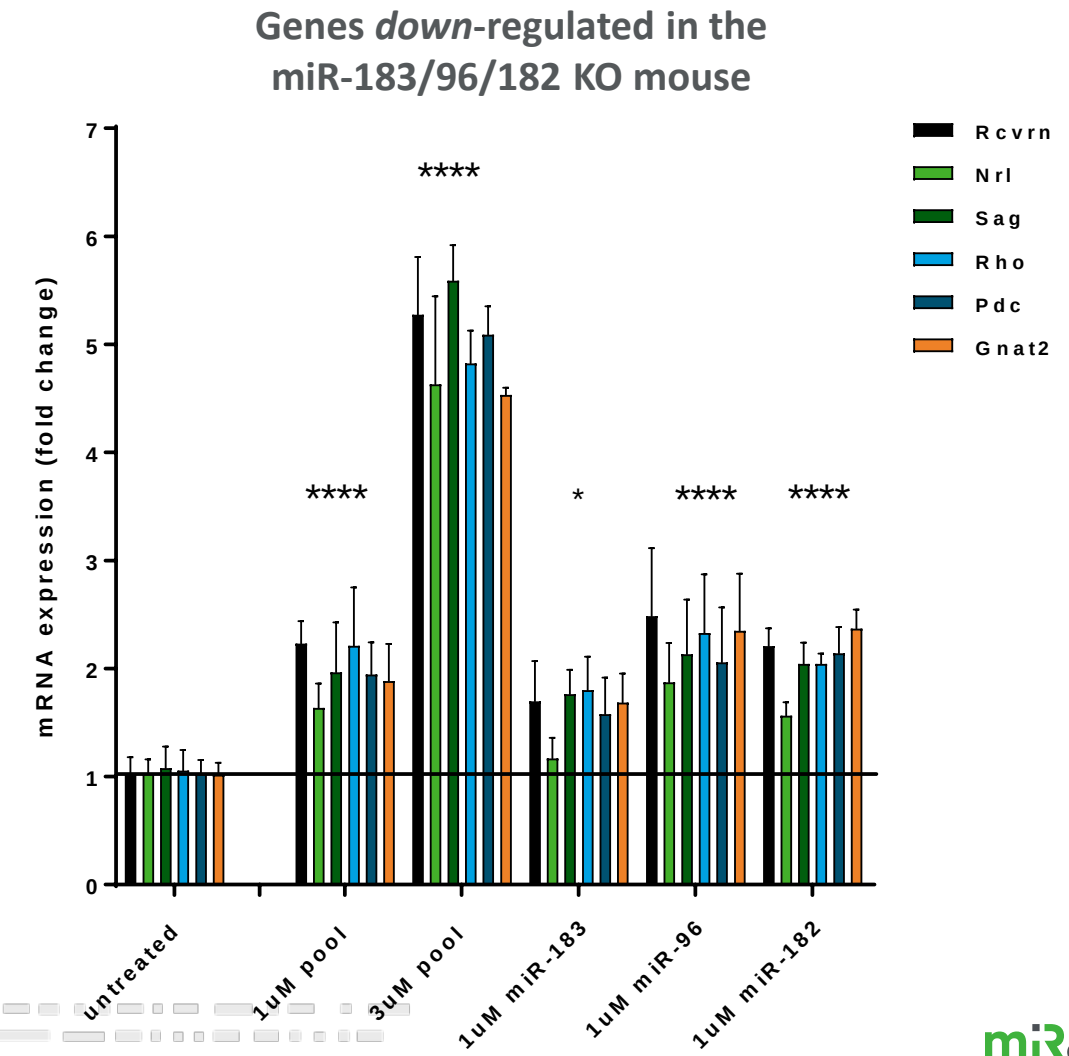
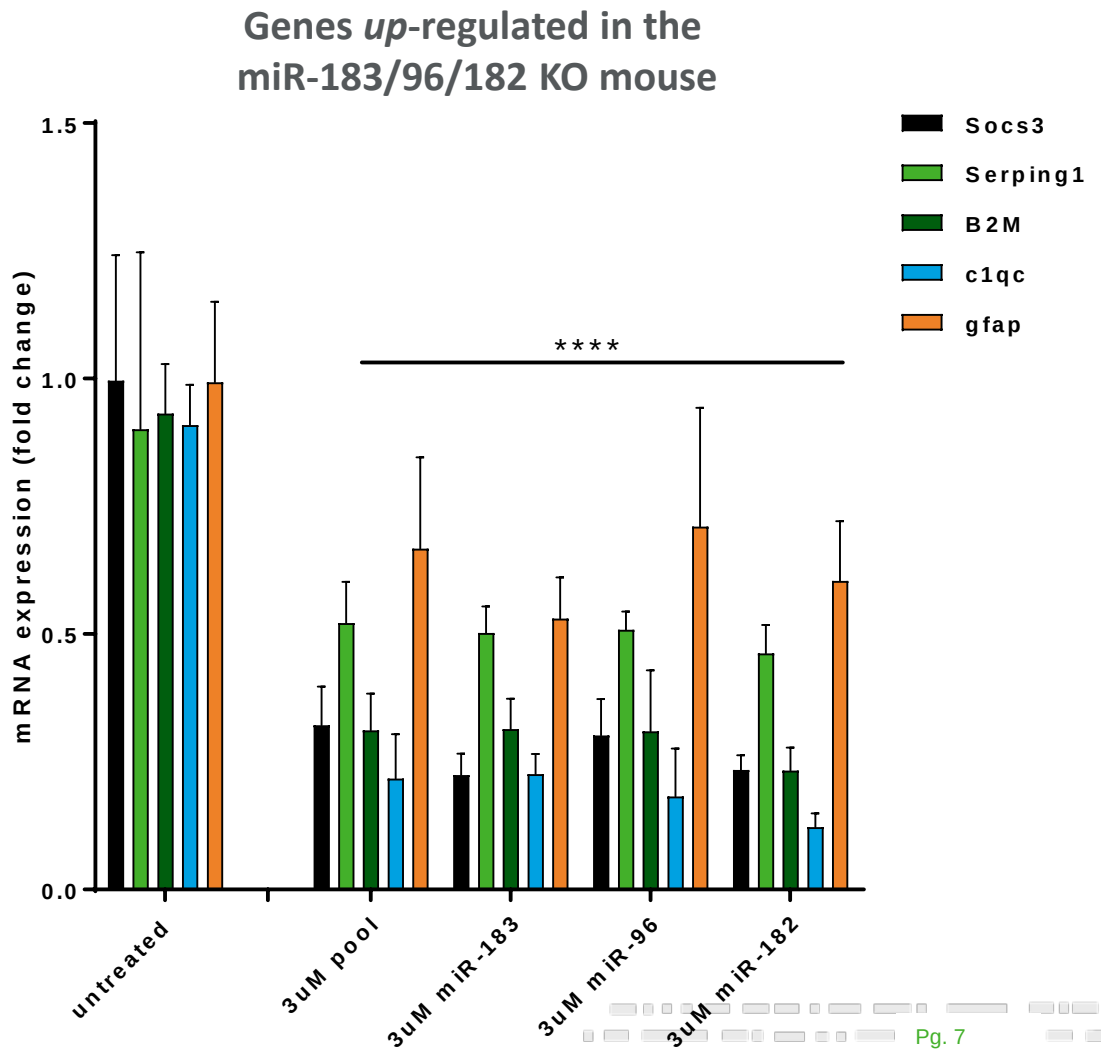
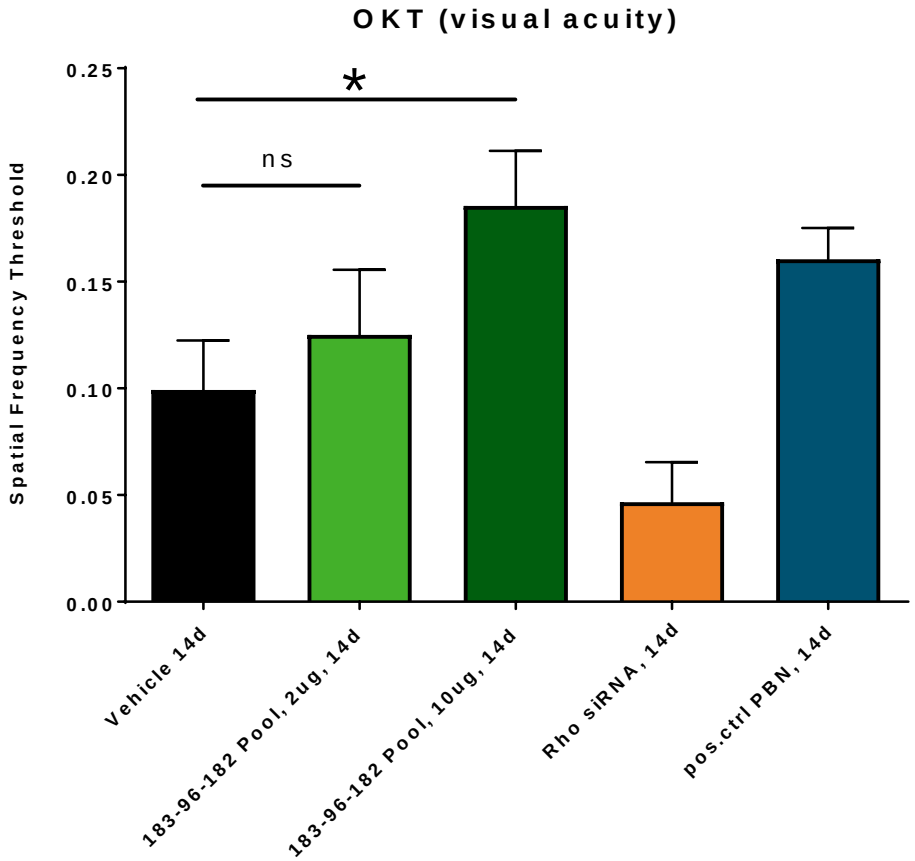
Treatment with miR-183/96/182 Reverses the Phototransduction Gene Signature of the KO Mouse

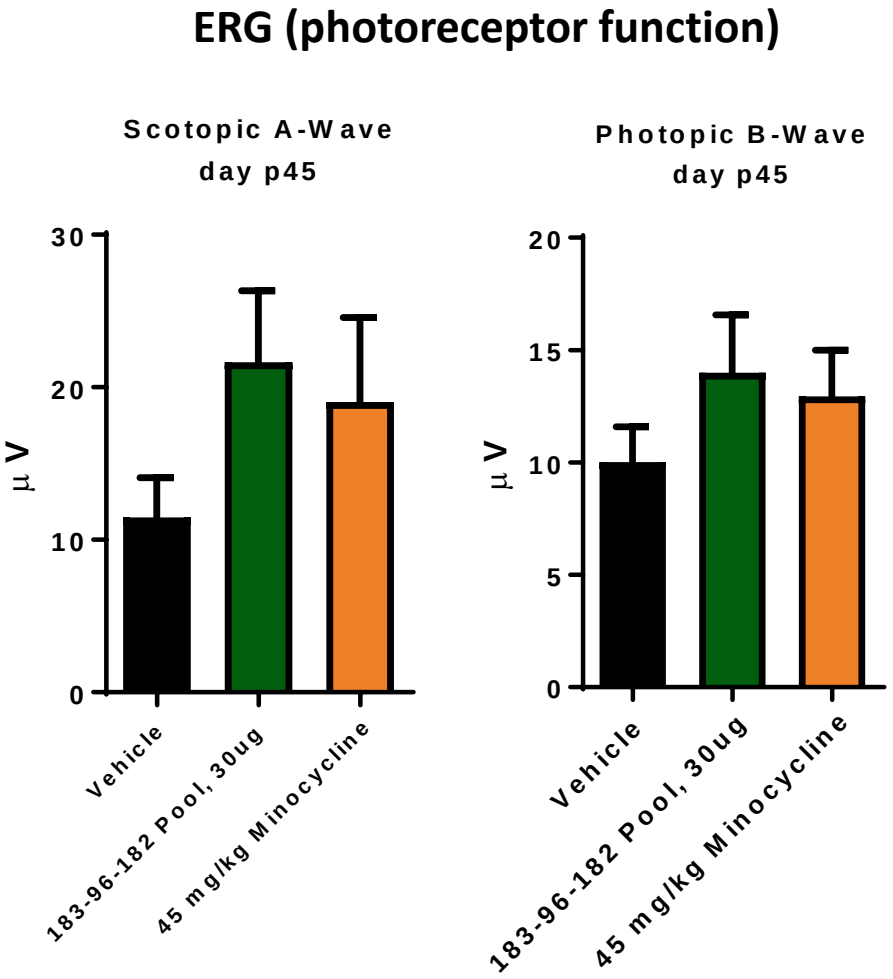
Primary rat retinal cells in vitro





miR182/183/96 Cluster Mimic in the Rd10 Mouse Model of Retinitis Pigmentosa





IVT injection of miR-183/96/182 pool shows efficacy with regard to visual acuity and photoreceptor function

Conclusions for miR-183 Cluster in RP

- Genetic modulation validates the miR-183 cluster as a therapeutic target for retinal degeneration
- Pharmacologic replacement of the miR-183 cluster modulates downstream biology including phototransduction genes
- We can functionally deliver microRNA modulators to the eye, including retina and photoreceptors, *in vivo*
- miR-183 cluster microRNA drugs trigger functional improvement of photoreceptors and vision in a mouse model of RP
- Mimicking activity of the microRNAs in the miR-183 cluster has therapeutic potential for retinal degeneration

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