Allele-selective Reduction Of Rho P23H-mutant Rhodopsin Rescues Phenotype Associated With Retinitis Pigmentosa In Preclinical Models

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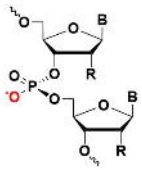
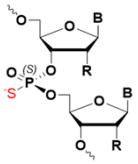
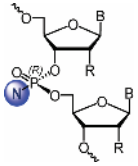
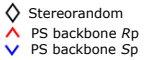
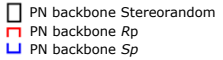
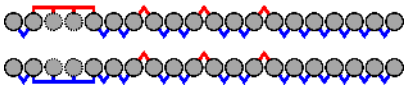
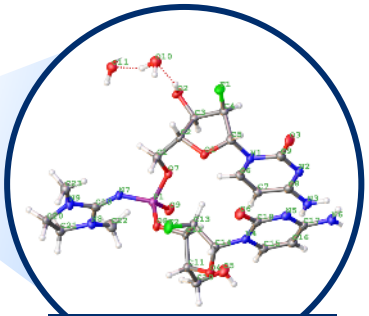
Expanding repertoire of backbone modifications with novel PN backbone chemistry

Backbone linkages

	PO	PS	PN
Backbone modification (X)	Phosphodiester 	Phosphorothioate 	Phosphoramidate diester 
Stereochemistry	Not chiral	Chiral 	Chiral 
Charge	Negative	Negative	Neutral
Depiction			
PRISM backbone modifications	PO/PS PO/PS/PN		

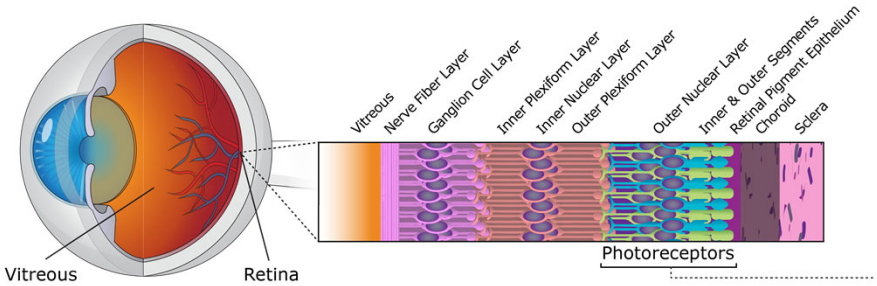


Phosphoryl guanidine x-ray structure

Molecule structure illustrative of backbone modification patterns

Autosomal dominant retinitis pigmentosa (adRP) associated with Rhodopsin P23H mutation

- Retinitis pigmentosa (RP) is a group of rare, genetic disorders of the eye resulting in progressive photoreceptor cell death and gradual functional loss
- Currently no cure for RP
- Rhodopsin accounts for >25% of adRP cases
- Approximately half of the RHO-associated adRP cases are caused by the P23H mutation
- Mutant P23H rhodopsin protein is thought to misfold and co-aggregate with wild-type rhodopsin, resulting in a gain-of-function or dominant negative effect in rod photoreceptor cells
- **~1,800 patients in US**



Allele-selective reduction of the mutant P23H allele while maintaining the wild type rhodopsin allele may prevent further cell loss.

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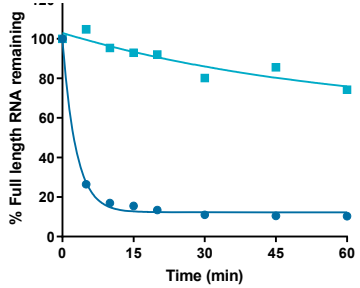
Stereopure oligo activity leads to preservation of rod cells *in vivo*

Allele-selective biochemically

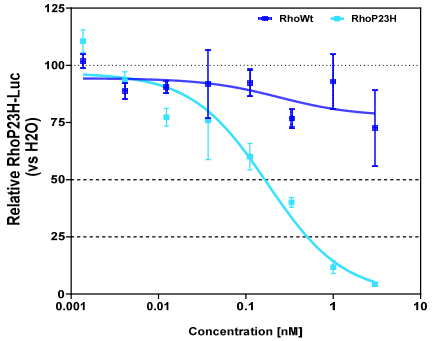
Stereopure

- Mutant RNA + **PS/PO oligo** + RNase H enzyme
- Wild-type RNA + **PS/PO oligo** + RNase H enzyme

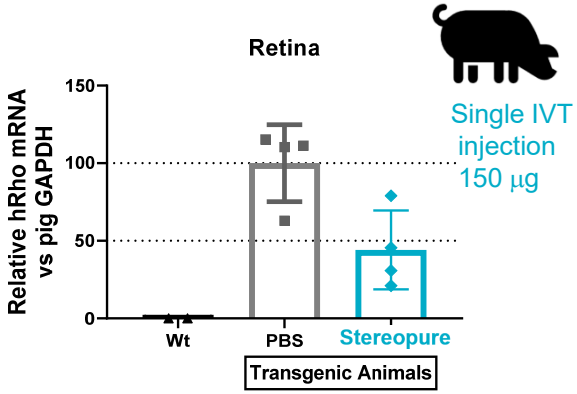


Allele-selective *in vitro*

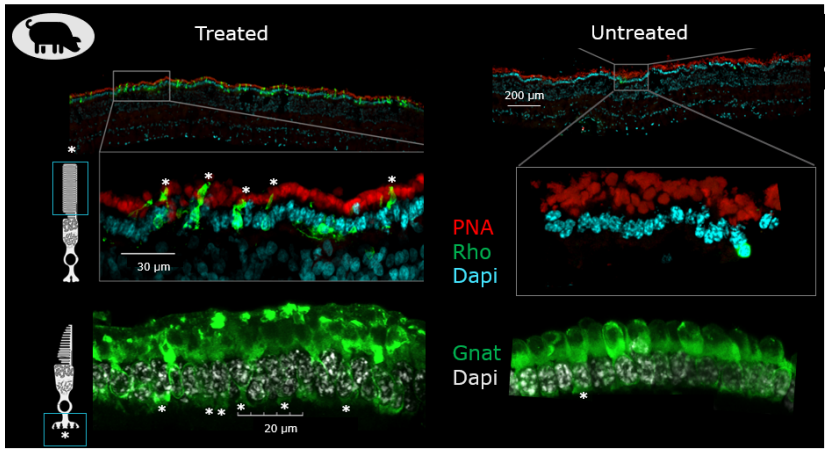
Stereopure



Active *in vivo*



Single injection (25 µg) retains rods/outer segments, cones/outer segments & pedicles 16 wks post-injection



adRP associated with Rhodopsin P23H mutation

Single 25 μg injection of **PN-containing oligo** retains outer **nuclear layer thickness** and **retinal cell function** through **8 wks** post-injection

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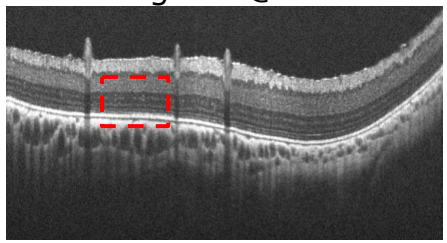
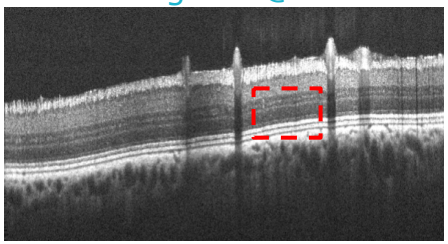
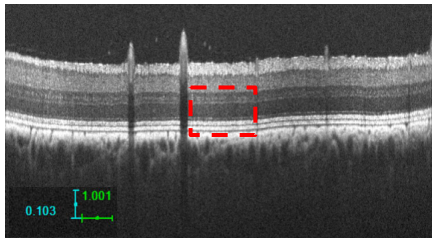
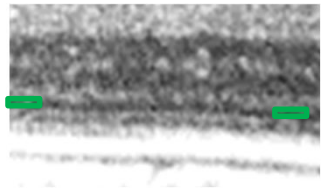
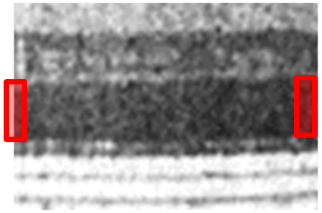
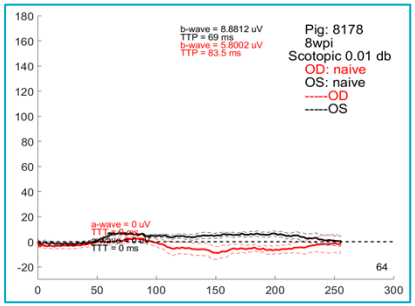
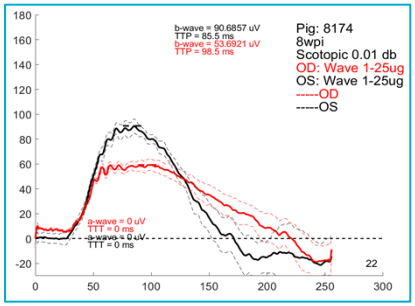
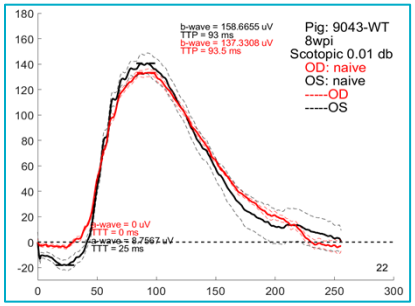
	Untreated Transgenic @ 8wks	Treated Transgenic @ 8 wks	Wild-type
OCT			
			
ERG			

Conclusion

- PN-containing oligonucleotides **preserve retinal cell morphology**, **prevent rod cell death** and **restore rod cell function** in severe humanized pig model of adRP
- PN-containing oligonucleotides represent a promising therapeutic option for the treatment of RHO P23H-dependent adRP and other diseases of the retina
- Longer timepoints are being evaluated

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