Stereopure oligonucleotides for potential treatment of inherited retinal disorders

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Forward-looking statements

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Targeting genetically defined diseases with stereopure oligonucleotides

Building fully integrated genetic medicines company led by neurology development programs

Neuromuscular

- ***Lead clinical program:*** **Investigational Suvodirsen Phase 2/3 trial, DYSTANCE 51, initiated in July 2019 for DMD (exon 51); program on development path toward US and global approvals**
- Advancing additional exon skipping candidates for DMD
- Commercialization activities underway

100% global rights

CNS

- ***Lead clinical program:*** **Two Phase 1b/2a trials ongoing for Huntington's disease using differentiated allele-selective approach**
- Advancing C9orf72 candidate for ALS and FTD
- SNP3 (HD) and ATXN3 (SCA3)

Takeda 50:50 option

Ophthalmology

- Initial candidate selection ongoing for inherited retinal diseases

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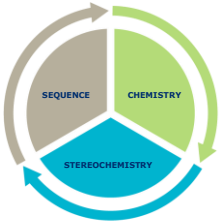
PRISM™

DESIGN & OPTIMIZE



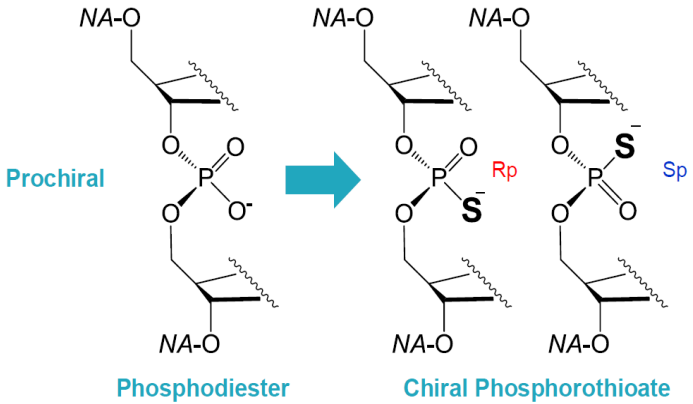
Stereopure oligonucleotides across multiple therapeutic modalities

Antisense | RNAi | Splicing

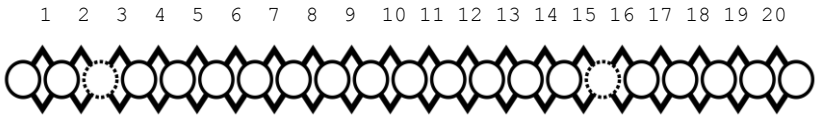
Stereopure oligonucleotides

Phosphorothioate (PS) modifications introduce chiral centers

An enormous number of permutations exist (2^n), often resulting in over 500,000 different molecules in every dose



Stereorandom ASO



2^{20} = 1,048,576 diastereoisomers

Stereopure ASO

1 diastereoisomer

Nucleotide

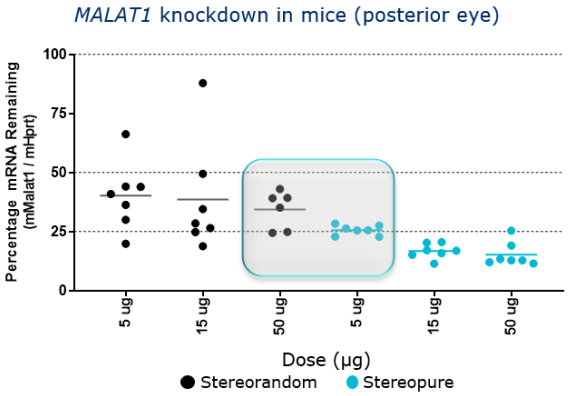
Stereorandom

*R*p

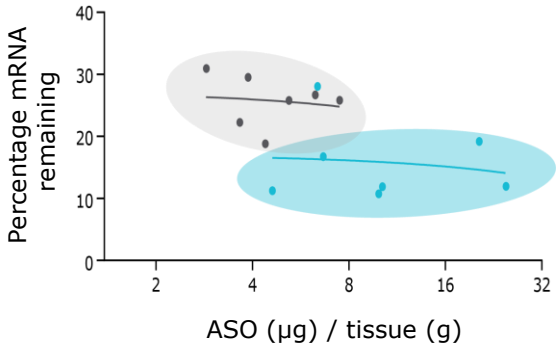
*S*p

Stereopure oligos have improved activity and duration *in vivo*

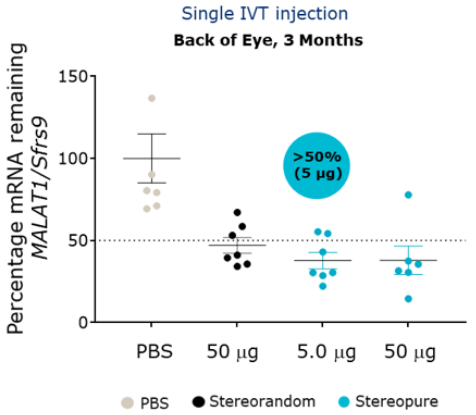
Improved potency in vivo



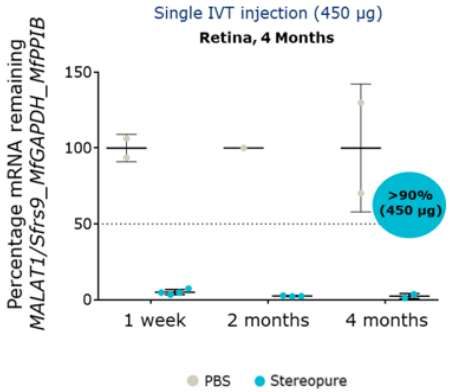
Improved PD/PK profile

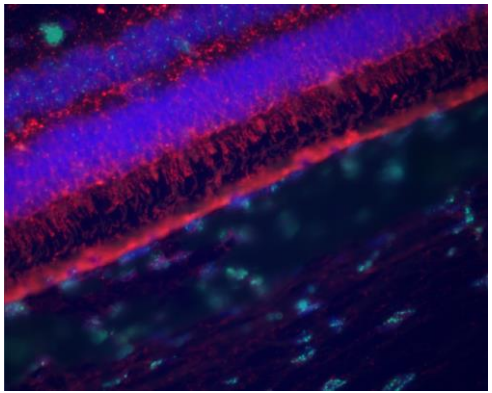


Improved Duration



NHP sustained duration and distribution





Cell Nuclei
Oligonucleotide
MALAT1 RNA

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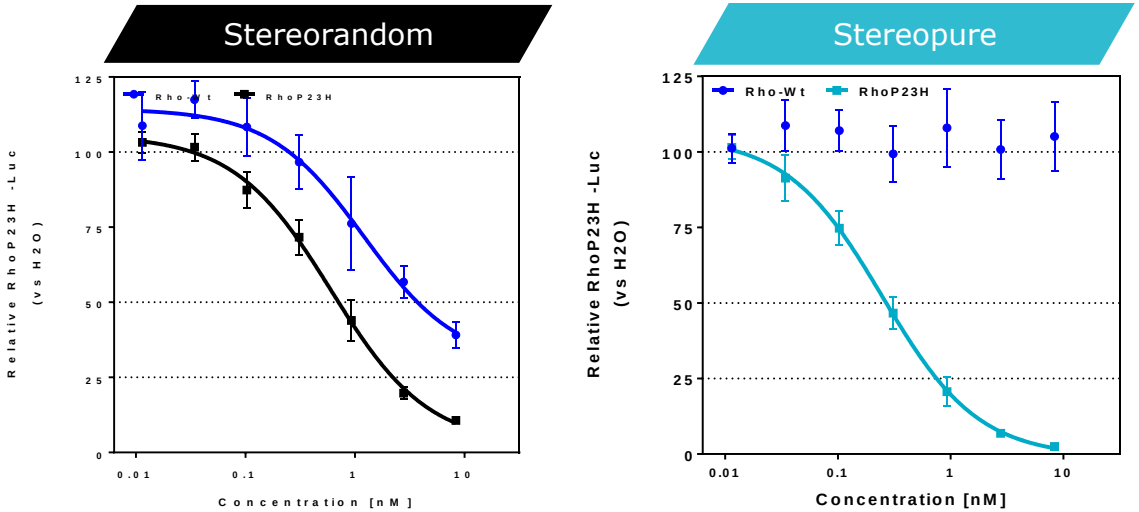
adRP associated with Rhodopsin P23H mutation

Stereopure oligonucleotides achieve allele-selective reduction of SNP-containing allele

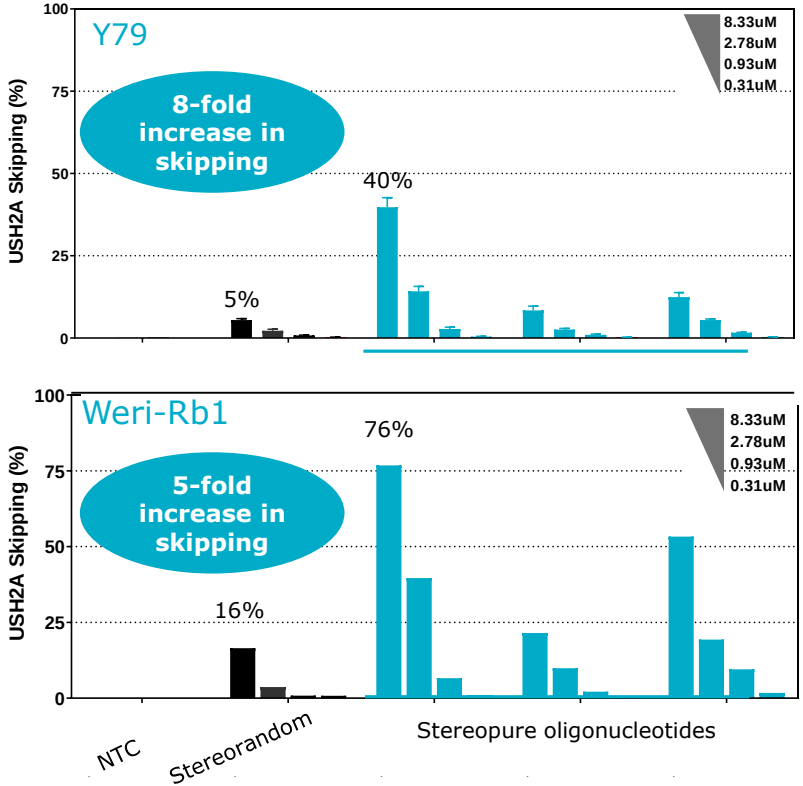


Stereopure ASO is allele selective compared with stereorandom

Reporter assays on a Wave stereopure sequence as well as a sequence described in WO2016138353A1: ASO and luciferase reporter plasmids (wild-type and mutant rhodopsin) are transfected into Cos7 cells. 48-hours later, cells are harvested and relative luminescence is measured.

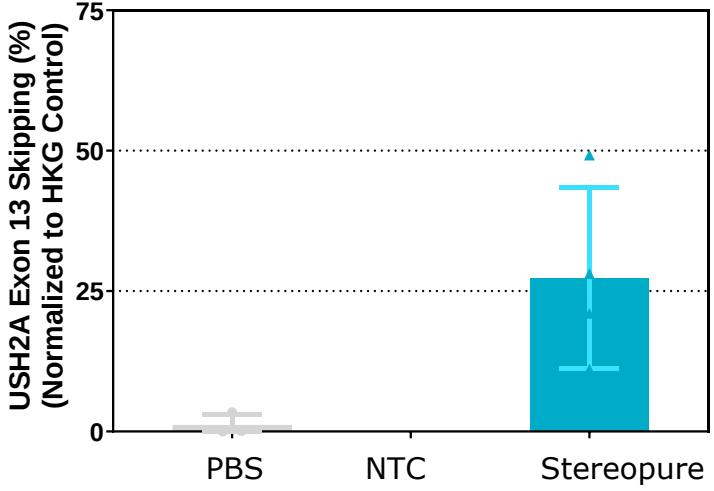
Usher syndrome: Exon-skipping approach

Stereopure oligonucleotides enhance exon skipping compared with stereorandom



ASOs were applied to Y79 and Weri-rb1 cell lines with no delivery vehicle. 48 hours post treatment cells were harvested and RNA was isolated. Exon skipping was calculated by [skipped/(unskipped+skipped)]*100. NTC= Non-targeting control, stereopure oligonucleotide. Stereorandom: oligo described in WO2018055134A1 Stereopure: Wave identified sequences with stereochemistry

Target engagement in human retina *ex vivo*



Whole eyes were enucleated and immediately placed in DMEM 10% FBS, 1% pen strep. 15-24hrs post enucleation, eyes were dissected and retina pieces of approximate equal size were added to a 96-well dish containing DMEM 10% FBS, 1% pen strep. Retinal pieces were treated with 20 uM of oligo for 48 hours. RNA was extracted and skipping was calculated. NTC= Non-targeting control, stereopure oligonucleotide.

Summary

- Oligonucleotides allow for intravitreal (IVT) injection with distribution across the retina to cell types of interest; targeting twice per year dosing
- Stereopure oligonucleotides open up novel strategies in both dominant and recessive IRDs; potential for potent and durable effect with low immune response

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THANK YOU

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