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Wave Life Sciences

Corporate Presentation

August 10, 2020

Forward-looking statements

This document contains forward-looking statements. All statements other than statements of historical facts contained in this document, including statements regarding possible or assumed future results of operations, preclinical and clinical studies, business strategies, research and development plans, collaborations and partnerships, regulatory activities and timing thereof, competitive position, potential growth opportunities, use of proceeds and the effects of competition are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause the actual results, performance or achievements of Wave Life Sciences Ltd. (the "Company") to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "expect," "plan," "aim," "anticipate," "could," "intend," "target," "project," "contemplate," "believe," "estimate," "predict," "potential" or "continue" or the negative of these terms or other similar expressions. The forward-looking statements in this presentation are only predictions. The Company has based these forward-looking statements largely on its current expectations and projections about future events and financial trends that it believes may affect the Company's business, financial condition and results of operations. These forward-looking statements speak only as of the date of this presentation and are subject to a number of risks, uncertainties and assumptions, including those listed under Risk Factors in the Company's Form 10-K and other filings with the SEC, some of which cannot be predicted or quantified and some of which are beyond the Company's control. The events and circumstances reflected in the Company's forward-looking statements may not be achieved or occur, and actual results could differ materially from those projected in the forward-looking statements. Moreover, the Company operates in a dynamic industry and economy. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties that the Company may face. Except as required by applicable law, the Company does not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

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Building a leading genetic medicines company

INNOVATIVE PLATFORM

- Stereopure oligonucleotides
- Backbone modifications
- Allele-selectivity
- Novel modalities (ADAR)
- Foundational stereochemistry IP

FOUNDATION OF NEUROLOGY PROGRAMS

- Huntington’s disease
- ALS / FTD
- Ataxias
- Parkinson’s disease
- Alzheimer’s disease

PRISM™

CLINICAL DEVELOPMENT EXPERTISE

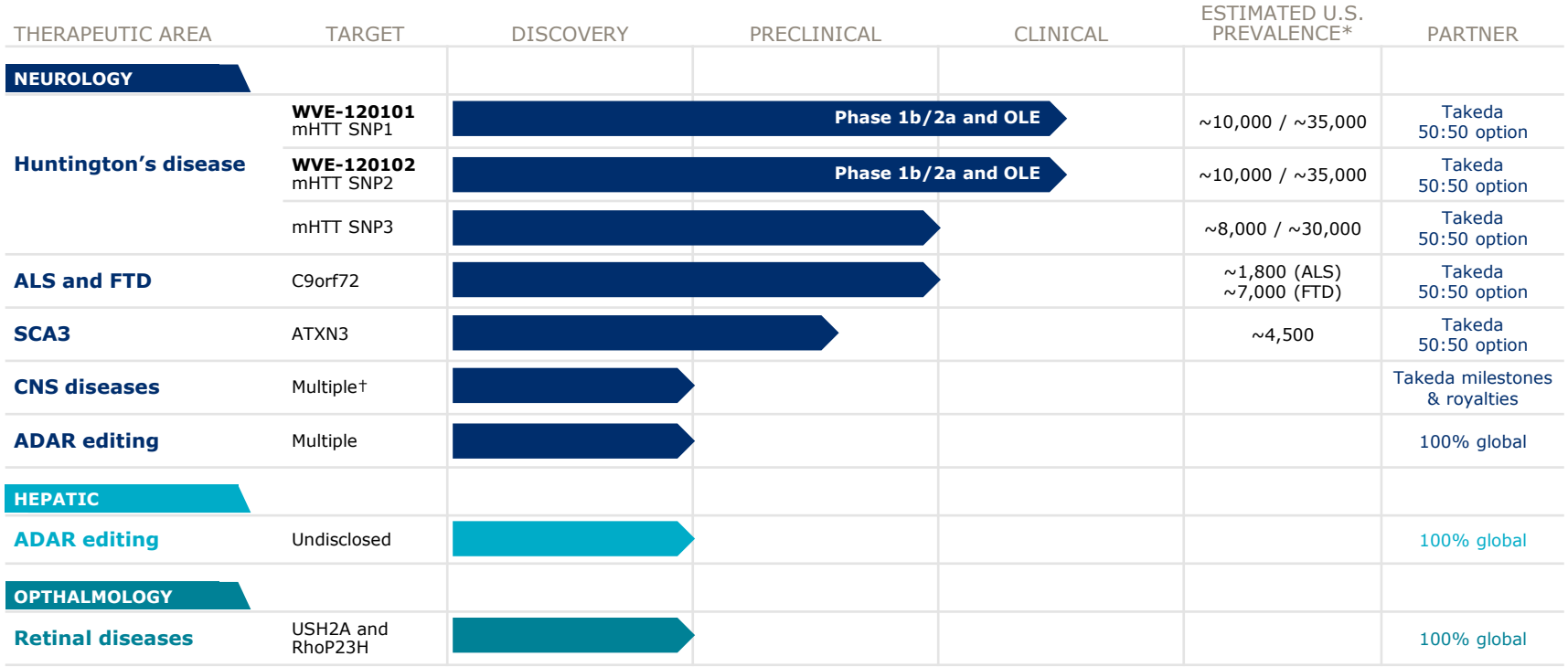
- Multiple global clinical trials ongoing across eight countries
- Innovative trial designs

MANUFACTURING

- Established internal manufacturing capabilities to produce oligonucleotides at scale

ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia

Innovative pipeline led by neurology programs



*Estimates of U.S. prevalence and addressable population by target based on publicly available data and are approximate; for Huntington's disease, numbers approximate manifest and pre-manifest populations, respectively.
†During a four-year term, Wave and Takeda may collaborate on up to six preclinical targets at any one time.
ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; SCA3: Spinocerebellar ataxia 3 CNS: Central nervous system; OLE: Open-label extension

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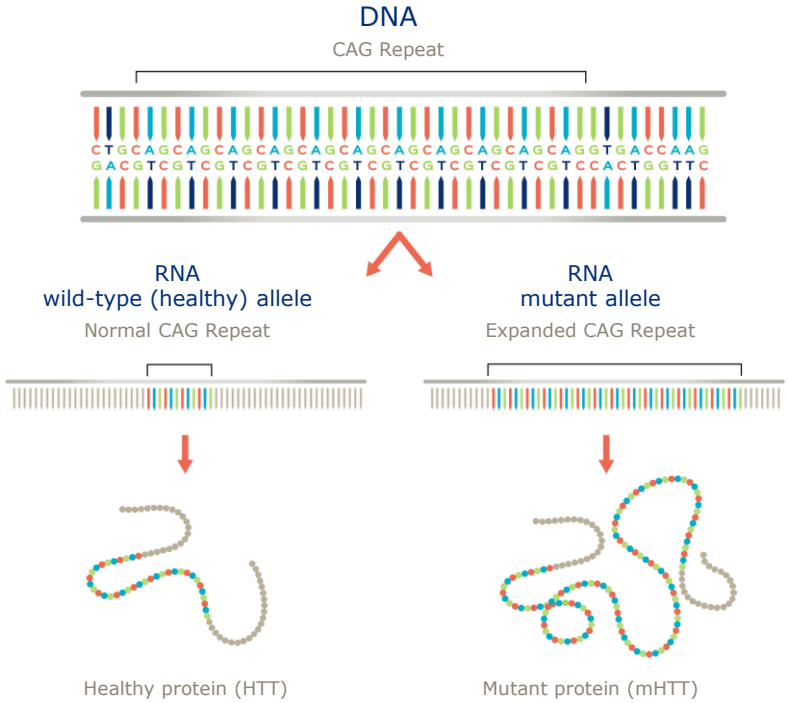
HD portfolio
Huntington's Disease

Huntington's disease: a hereditary, fatal disorder

- Autosomal dominant disease, characterized by cognitive decline, psychiatric illness and chorea; fatal
- No approved disease-modifying therapies
- Expanded CAG triplet repeat in HTT gene results in production of mutant huntingtin protein (mHTT); accumulation of mHTT causes progressive loss of neurons in the brain
- Wild-type (healthy) HTT protein critical for neuronal function; evidence suggests wild-type HTT loss of function plays a role in Huntington's disease
- 30,000 people with Huntington's disease in the US; another 200,000 at risk of developing the condition



Sources: Auerbach W, et al. *Hum Mol Genet.* 2001;10:2515-2523. Dragatsis I, et al. *Nat Genet.* 2000;26:300-306. Leavitt BR, et al. *J Neurochem*. 2006;96:1121-1129. Nasir J, et al. *Cell*. 1995;81:811-823. Reiner A, et al. *J Neurosci.* 2001;21:7608-7619. White JK, et al. *Nat Genet*. 1997;17:404-410. Zeitlin S, et al. *Nat Genet*. 1995;11:155-163. Carroll JB, et al. *Mol Ther.* 2011;19:2178-2185. HDSA 'What is Huntington's disease?' https://hdsa.org/what-is-hd/overview-of-huntingtons-disease/ Accessed: 11/2/18.; Becanovic, K., et al., Nat Neurosci, 2015. 18(6): p. 807-16. Van Raamsdonk, J.M., et al., Hum Mol Genet, 2005. 14(10): p. 1379-92.; Van Raamsdonk, J.M., et al., BMC Neurosci, 2006. 7: p. 80.

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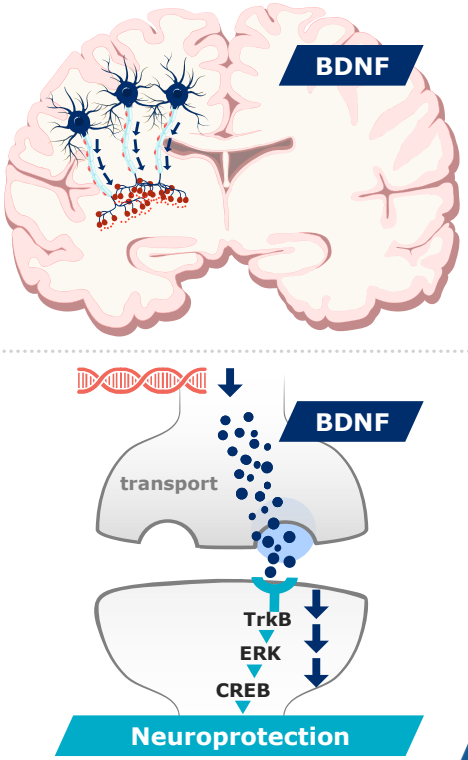
Importance of wild-type huntingtin (wtHTT) in HD

Huntington's disease (HD) may be caused by a dominant gain of function in mutant HTT *and* a loss of function of wtHTT protein

- Evidence suggests wild-type or healthy HTT is neuroprotective in an adult brain
  - Transport of key neurotrophic factors such as brain-derived neurotrophic factor (BDNF) are regulated by wtHTT levels
- Relative proportion of wild-type to mutant protein is critical
  - Increased amount of wild-type protein relative to mutant HTT may result in slower disease progression (measured by age-at-onset)
  - Patients with lack of wild-type have significantly more severe disease (measured by disease progression after symptom onset)



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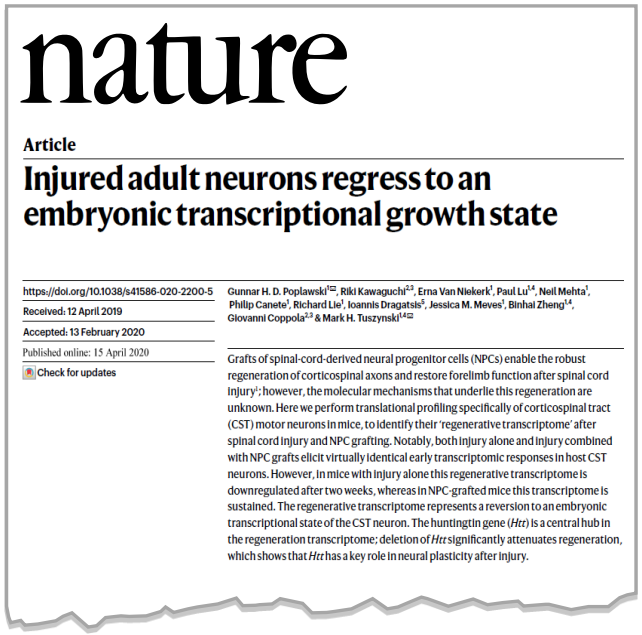
Sources: Van Raamsdonk, J.M., et al., Hum Mol Genet, 2005; Van Raamsdonk, J.M., et al., BMC Neurosci, 2006; Becanovic, K., et al., Nat Neurosci, 2015; Saudou, F. and S. Humbert, The Biology of Huntingtin. Neuron, 2016; Gauthier, L.R., et al., Cell, 2004; Caviston, J.P. and E.L. Holzbaur, Trends Cell Biol, 2009; Ho, L.W., et al., J Med Genet, 2001, Zuccato et al., Science 2001; Zuccato et al., Brain Pathol 2007; Marullo et al. Genome Biol 2010; Squitieri et. al, Brain 2003

Nature publication contributes to weight of evidence on importance of wild-type huntingtin



nature

Article

Injured adult neurons regress to an embryonic transcriptional growth state

https://doi.org/10.1038/s41586-020-2200-5
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Accepted: 13 February 2020
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Check for updates

Gunnar H. D. Poplawski[1✉], Riki Kawaguchi[2,3], Erna Van Niekerk[1], Paul Lu[1,4], Neil Mehta[1], Phillip Canete[1], Richard Lie[1], Ioannis Dragatsis[5], Jessica M. Meves[1], Binhai Zheng[1,4], Giovanni Coppola[2,3] & Mark H. Tuszynski[1,4✉]

Grafts of spinal-cord-derived neural progenitor cells (NPCs) enable the robust regeneration of corticospinal axons and restore forelimb function after spinal cord injury[1]; however, the molecular mechanisms that underlie this regeneration are unknown. Here we perform translational profiling specifically of corticospinal tract (CST) motor neurons in mice, to identify their 'regenerative transcriptome' after spinal cord injury and NPC grafting. Notably, both injury alone and injury combined with NPC grafts elicit virtually identical early transcriptomic responses in host CST neurons. However, in mice with injury alone this regenerative transcriptome is downregulated after two weeks, whereas in NPC-grafted mice this transcriptome is sustained. The regenerative transcriptome represents a reversion to an embryonic transcriptional state of the CST neuron. The huntingtin gene (*Htt*) is a central hub in the regeneration transcriptome; deletion of *Htt* significantly attenuates regeneration, which shows that *Htt* has a key role in neural plasticity after injury.

- Conditional knock-out of Htt in 4-month old mice (post-neuronal development)
- Results suggest that:
  1) Htt plays a central role in the regenerating transcriptome (potentially influencing genes such as NFKB, STAT3, BDNF)
  2) Htt is essential for regeneration

> **"Indeed, conditional gene deletion showed that Htt is required for neuronal repair. Throughout life, neuronal maintenance and repair are essential to support adequate cellular functioning"**

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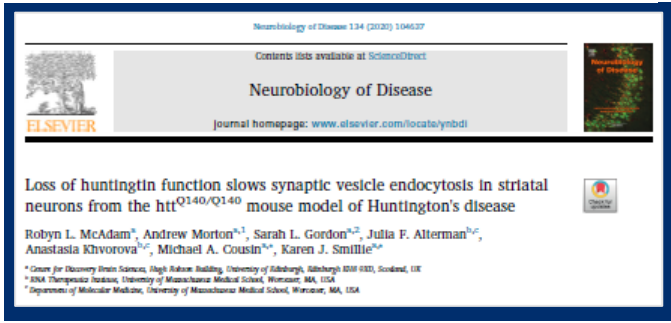
Poplawski et al., *Nature*, April 2019; Htt: Huntingtin protein

Increasing evidence on the importance of wtHTT in HD pathogenesis, CNS and systemic health

Recent publications on wtHTT LoF as a likely driver of HD pathogenesis


Neurobiology of Disease 134 (2020) 104637

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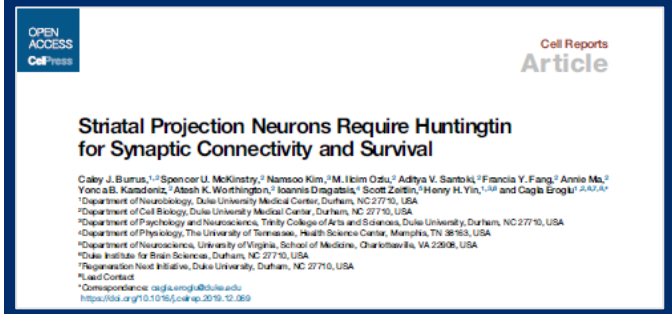
Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Loss of huntingtin function slows synaptic vesicle endocytosis in striatal neurons from the htt$^{Q140/Q140}$ mouse model of Huntington's disease

Robyn L. McAdam[a], Andrew Morton[a,1], Sarah L. Gordon[a,2], Julia F. Alterman[b,c], Anastasia Khvorova[b,c], Michael A. Cousin[a,*], Karen J. Smillie[a,*]

- Striatum-specific defect in synaptic vesicle endocytosis that was not corrected by total lowering of HTT
- Corrected by overexpression of wild-type protein


OPEN ACCESS CellPress

Cell Reports

Article

Striatal Projection Neurons Require Huntingtin for Synaptic Connectivity and Survival

Caley J. Burrus,[1,2] Spencer U. McKinstry,[2] Namsoo Kim,[3] M. Ilcim Ozlu,[2] Aditya V. Santoki,[2] Francia Y. Fang,[2] Annie Ma,[2] Yonca B. Karadeniz,[2] Atesh K. Worthington,[2] Ioannis Dragatsis,[4] Scott Zeitlin,[5] Henry H. Yin,[1,6,8] and Cagla Eroglu[1,2,6,7,9,*]

- Striatal projection neurons require HTT for motor regulation, synaptic development, cell health, and survival during aging
- Loss of HTT function could play a critical role in HD pathogenesis

wtHTT in HD highlighted at CHDI 15th Annual HD Therapeutics Conference:

HTT LOWERING: EXPLORING DISTRIBUTION, TIMING, AND SAFETY (LOSS OF FUNCTION)

Key points discussed at meeting:

- wtHTT has numerous critical functions throughout life (e.g., intracellular trafficking, cell-cell adhesion, BDNF transport)
- Near elimination of mouse wtHtt detrimental regardless of when suppression begins
- Specific brain regions, e.g., STN, may be particularly vulnerable to wtHTT lowering
- Mouse Htt lowering can lead to thalamic, hepatic, pancreatic toxicity
- HTT LoF mutations highly constrained in human population, suggesting selection against LoF mutations

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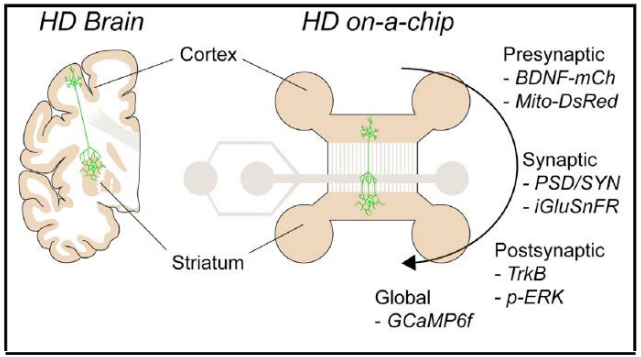
LoF: Loss of function; wtHTT: wild-type huntingtin; HD: Huntington's disease; STN: subthalamic nucleus

Wild-type HTT in the cortex appears critical for striatal health



Neuron Type	Genetic Status				Compartment
Cortical	WT	WT	HD	HD	Presynaptic
Striatal	WT	HD	HD	WT	Synaptic / Post-synaptic
Network Status	*Functional*		*Dysfunctional*		

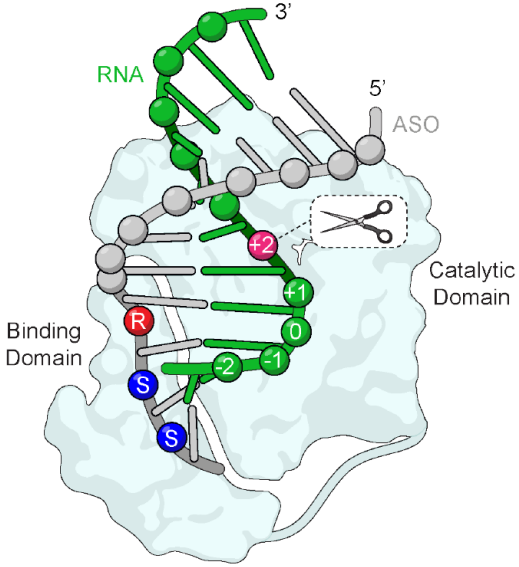
Status of the presynaptic compartment determines the integrity of the network

Presented by Dr. Frederic Saudou at Wave's Analyst and Investor Research Day on October 7, 2019
Virlogeux et al., Cell Reports 2018

Wave approach: novel, allele-selective silencing

Aims to lower mHTT transcript while leaving healthy wild-type HTT relatively intact

- Utilize association between single nucleotide polymorphisms (SNPs) and genetic mutations to specifically target errors in genetic disorders, including Huntington's disease (HD)
- Potential to provide treatment for up to 80% of HD population



RNase H and ASO:RNA

Allele-selectivity possible by targeting SNPs associated with expanded long CAG repeat in HTT gene

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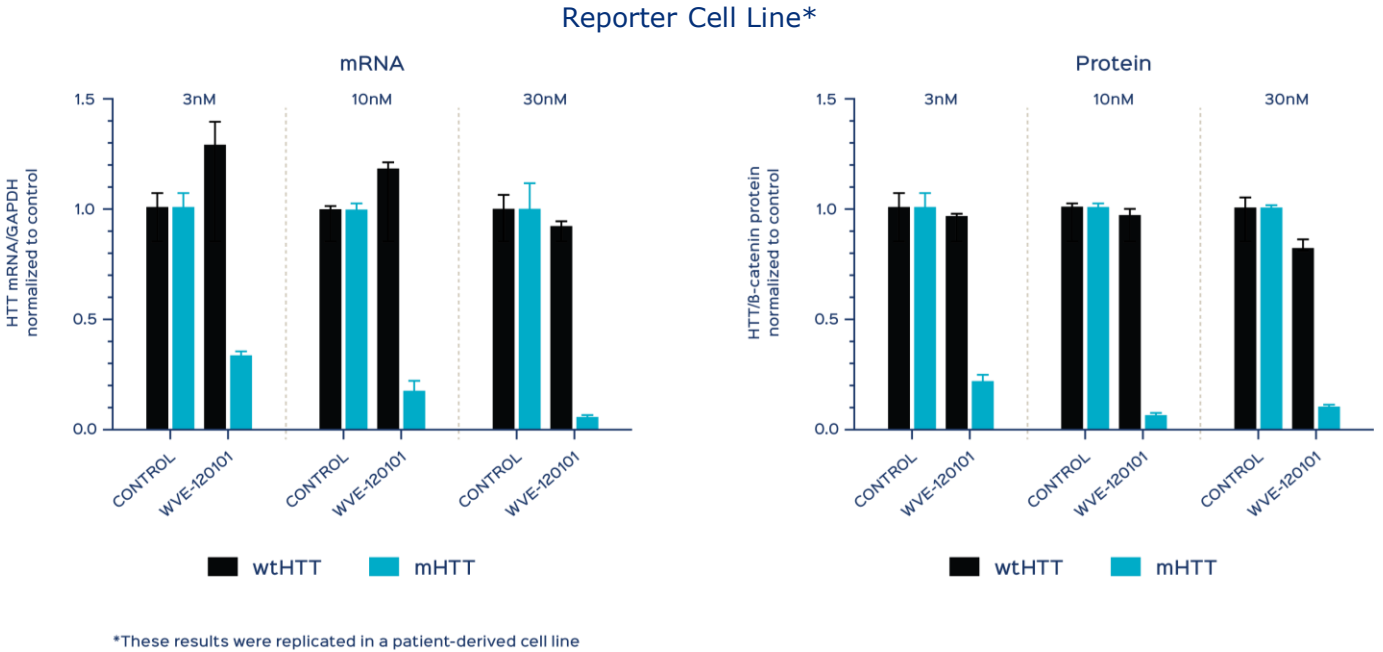
Source: Kay, et al. Personalized gene silencing therapeutics for Huntington disease. *Clin Genet.* 2014;86:29–36.

Selective reduction of mHTT mRNA & protein

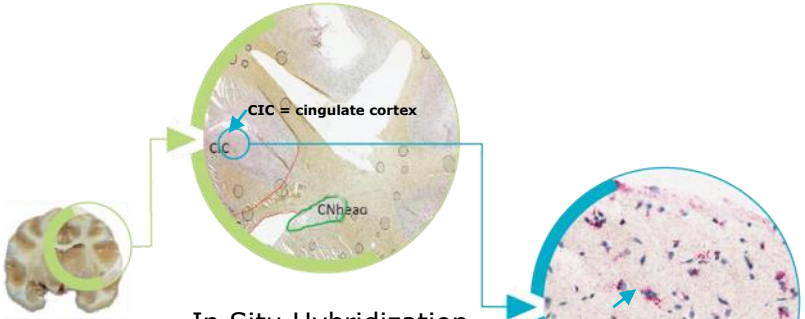


*These results were replicated in a patient-derived cell line

Source: Meena, Zboray L, Svrzikapa N, et al. Selectivity and biodistribution of WVE-120101, a potential antisense oligonucleotide therapy for the treatment of Huntington's disease. Paper presented at: 69th Annual Meeting of the American Academy of Neurology; April 28, 2017; Boston, MA.

Demonstrated delivery to brain tissue

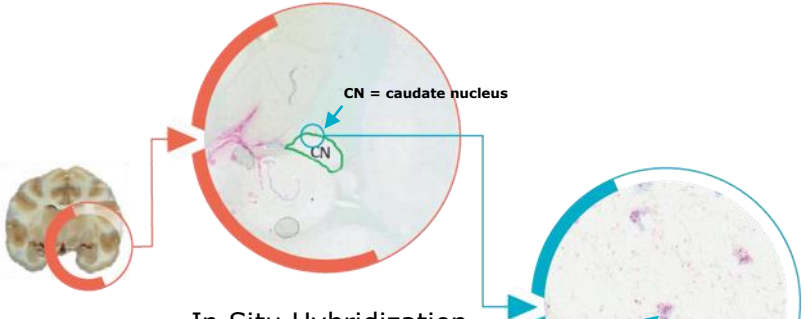
- WVE-120101 and WVE-120102 distribution in cynomolgus non-human primate brain following intrathecal bolus injection



In Situ Hybridization ViewRNA stained tissue

Red dots are WVE-120101 oligonucleotide

Arrow points to nuclear and perinuclear distribution of WVE- 120101 in cingulate cortex



In Situ Hybridization ViewRNA stained tissue

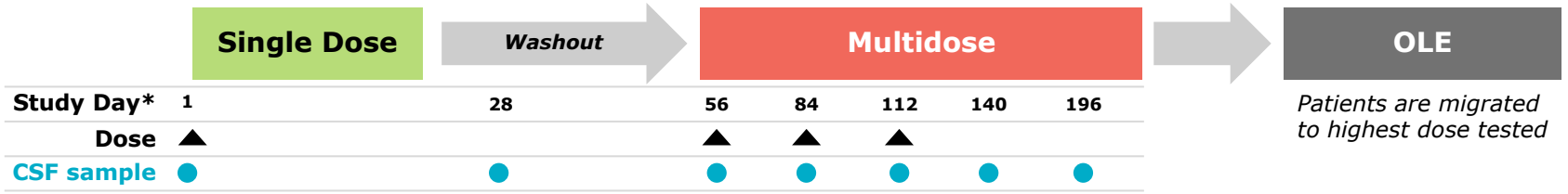
Red dots are WVE-120102 oligonucleotide

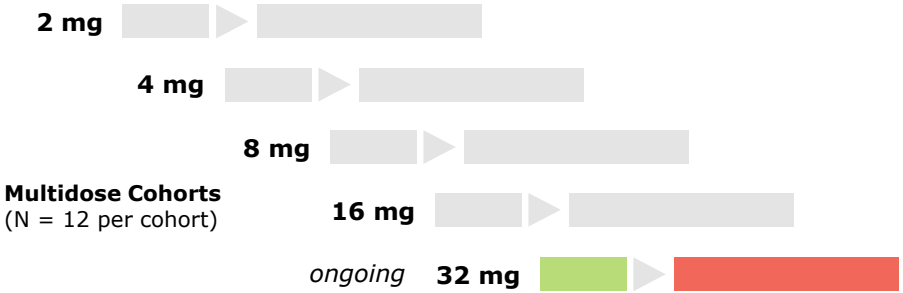
Arrow points to nuclear and perinuclear distribution of WVE-120102 in caudate nucleus

Source: Meena, Zboray L, Svrzikapa N, et al. Selectivity and biodistribution of WVE-120101, a potential antisense oligonucleotide therapy for the treatment of Huntington's disease. Paper presented at: 69th Annual Meeting of the American Academy of Neurology; April 28, 2017; Boston, MA.

PRECISION-HD clinical trials

Two Phase 1b/2a clinical trials for WVE-120101 and WVE-120102





PRECISION-HD2 interim data
(2-16 mg cohorts pooled)

- **Safety profile** supported addition of higher dose cohorts

Biomarker Effects

- **Reduction in mHTT** (-12.4%[1]); Analysis across groups suggests dose response at highest doses[3]
- **No change in total HTT**
- Not all patients had reached Day 140 at interim analysis

PRECISION-HD2 and PRECISION-HD1 data, including 32 mg cohorts and OLE data, expected in 1Q 2021

OLE: Open label extension; CSF: cerebrospinal fluid; mHTT: mutant huntingtin; wtHTT: wild-type HTT; tHTT: total HTT
* Study day may vary depending on patient washout period [1]Hodges-Lehmann non-parametric shift estimates of the difference between treatment and placebo, p<0.05 (Wilcoxon-Mann-Whitney non-parametric significance test); [3] Multiple Contrast Test (MCT), p=0.03; Interim data announced December 2019

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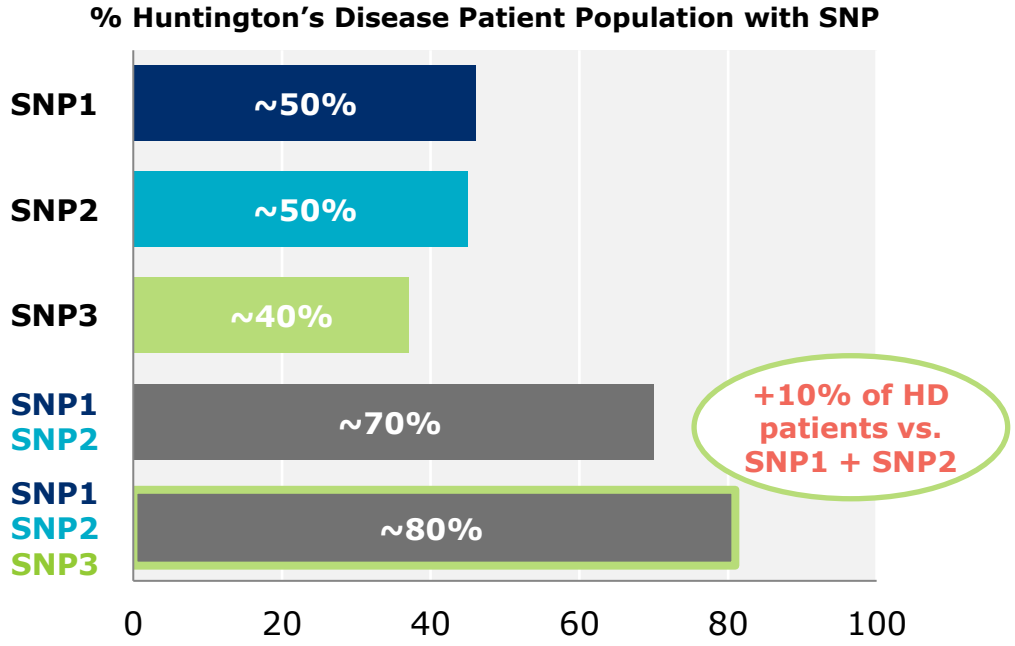
Three allele-selective HD programs

Potential to address ~80% of HD patient population



Intend to explore efficacy in early manifest and pre-manifest HD patient populations

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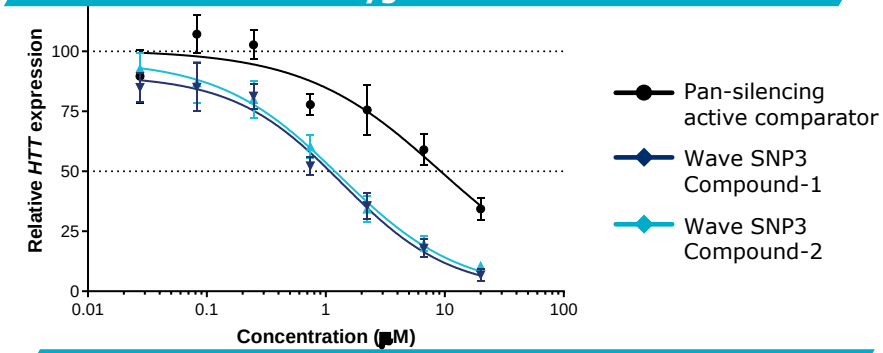
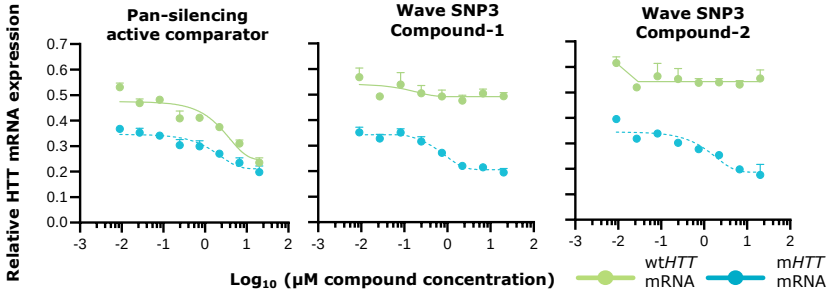
SNP3 program approaching clinical development

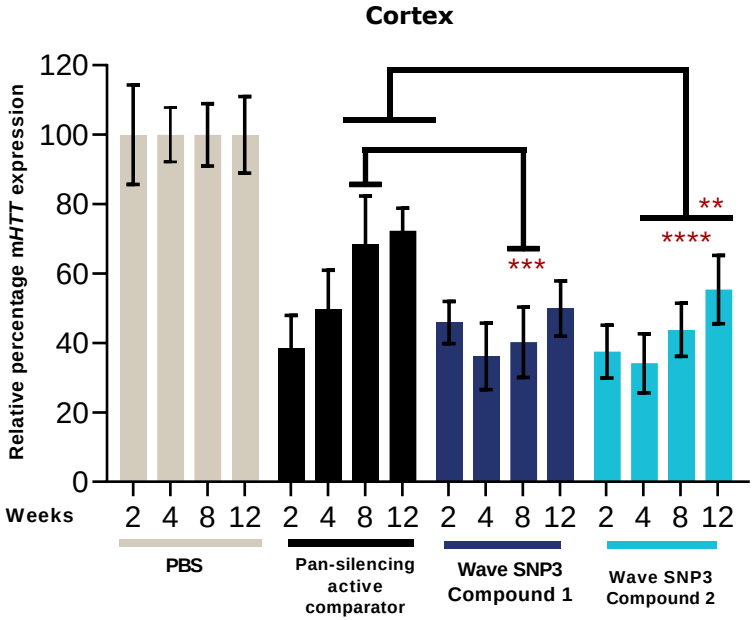
Potent mutant *HTT* knockdown activity in homozygous iCell neurons



No loss of selectivity with increasing concentrations



Knockdown persists for 12 weeks in BACHD mouse model



Similar knockdown achieved in striatum

Clinical development expected to initiate with CTA submission in 4Q 2020

Data presented at CHDI Foundation's 15th Annual HD Therapeutics Conference Feb 24-27, 2020; See poster for full dataset. CTA: clinical trial application

[Figure on right] Statistics: All oligo treatment groups statistically significantly different from PBS; One-way ANOVA ****, P≤0.0001. SNP3 Compound-1 and Compound-2 significantly different from pan-silencing active comparator at 8, 12 weeks ***, P<0.005; **P=0.001."

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C9orf72 program

Amyotrophic Lateral Sclerosis (ALS)

Frontotemporal Dementia (FTD)

C9orf72: a critical genetic risk factor

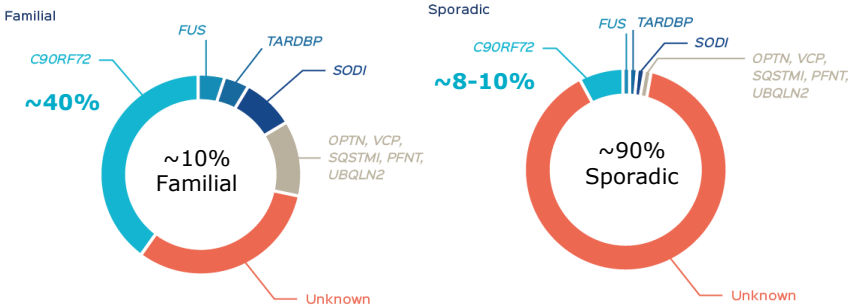
- C9orf72 gene provides instructions for making protein found in various tissues, with abundance in nerve cells in the cerebral cortex and motor neurons
- C9orf72 genetic mutations are the strongest genetic risk factor found to date for the more common, non-inherited (sporadic) forms of Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD); GGGGCC repeat drives the formation and accumulation of toxic RNA and dipeptide repeat proteins that accumulate in CNS tissue
- First pathogenic mechanism identified to be a genetic link between familial (inherited) ALS and FTD
- Most common mutation identified associated with familial ALS and FTD
- Measurement of dipeptide biomarker in CSF has potential to accelerate drug development

Source: DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. *Neuron.* 2011;72:245-256. Renton AE, Majounie E, Waite A, et al. *Neuron.* 2011;72:257-268.

Targeting patients with C9orf72 genetic mutations

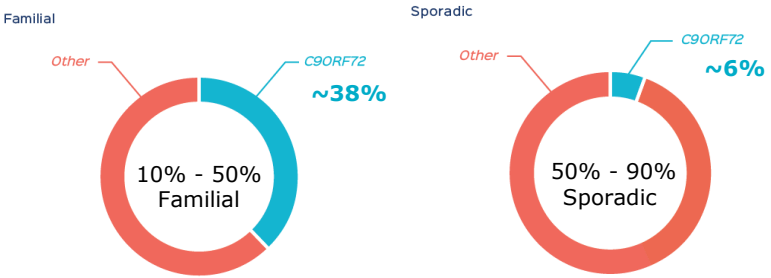
Amyotrophic lateral sclerosis (ALS)

- Fatal neurodegenerative disease; progressive degeneration of motor neurons in brain and spinal cord
- Affects ~15,000-20,000 people in US; Median survival of 3Y
- C9orf72 is present in ~40% of familial ALS and 8-10% of sporadic ALS; most common demonstrated mutation related to ALS



Frontotemporal dementia (FTD)

- Progressive neuronal atrophy with loss in frontal and temporal cortices; personality / behavioral changes, gradual impairment of language skills
- Affects ~55,000 people in the US; 2nd most common form of early-onset dementia in people <65 years
- Up to 50% of FTD patients have a family history of dementia



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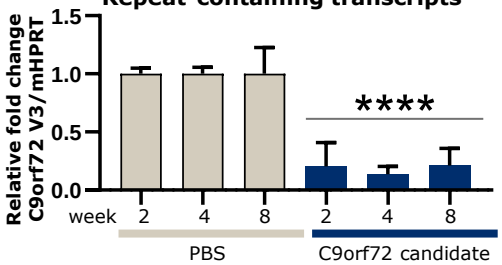
ALS: Renton AE, Chiò A, Traynor BJ. State of play in amyotrophic lateral sclerosis genetics. *Nat Neurosci*. 2014;17:17–23.; FTD: Stevens M, et al. Familial aggregation in frontotemporal dementia. *Neurology.* 1998;50:1541-1545. Majounie E, et al. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. *Lancet Neurol.* 2012;11:323-330.

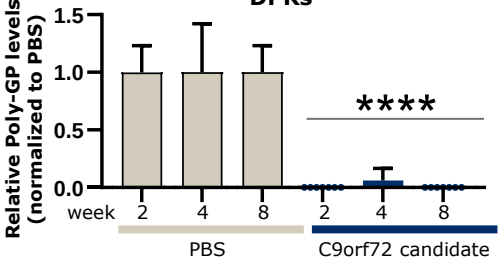
C9orf72 program: Selective silencing *in vivo* of expanded C9orf72 repeat transcripts and DPRs

- Hexanucleotide repeat drives the formation and accumulation of toxic RNA and dipeptide repeat proteins (DPRs) that accumulate in CNS tissue
- **Wave's approach:** Selectively silence the repeat containing transcript while minimizing the impact on C9orf72 protein

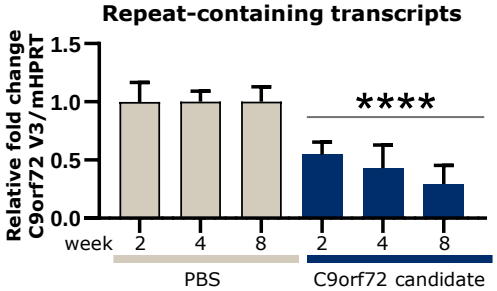
Potent *in vivo* knockdown of repeat containing transcripts and DPRs

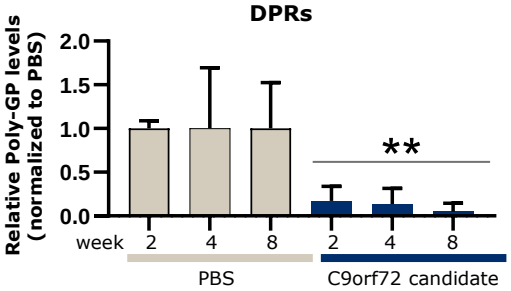
Spinal Cord



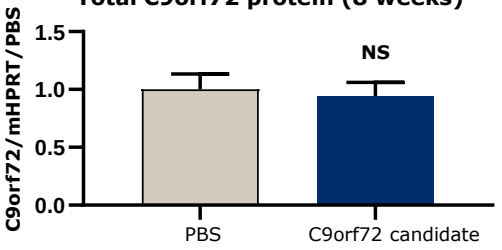


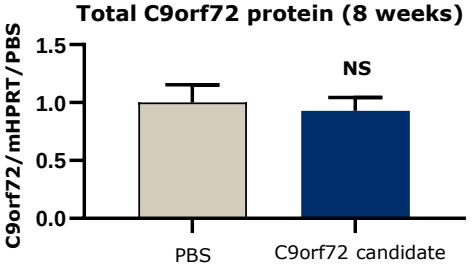
Cortex





Protein preservation





Clinical development expected to initiate with CTA submission in 4Q 2020

CTA: clinical trial application; Experimental description: 2 x 50 ug on day 1 and day 8; mRNA Samples were analyzed using quantitative PCR (Taqman assay), Protein samples were measured by Western Blot. Dipeptide repeat proteins were measured by Poly-GP MSD assay.

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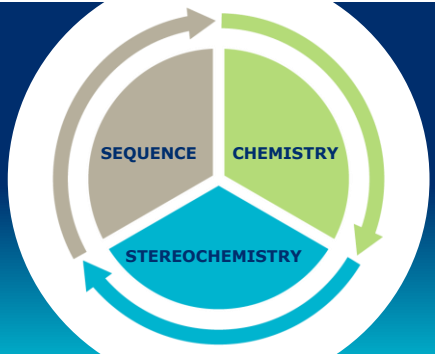
PRISM Platform

PRISM™

Enables Wave to target genetically defined diseases with stereopure oligonucleotides across multiple therapeutic modalities

DESIGN

Unique ability to construct stereopure oligonucleotides with one defined and consistent profile



OPTIMIZE

A deep understanding of how the interplay among oligonucleotide sequence, chemistry, and backbone stereochemistry impacts key pharmacological properties

Through iterative analysis of *in vitro* and *in vivo* outcomes and artificial intelligence-driven predictive modeling, Wave continues to define design principles that are deployed across programs to rapidly develop and manufacture clinical candidates that meet pre-defined product profiles

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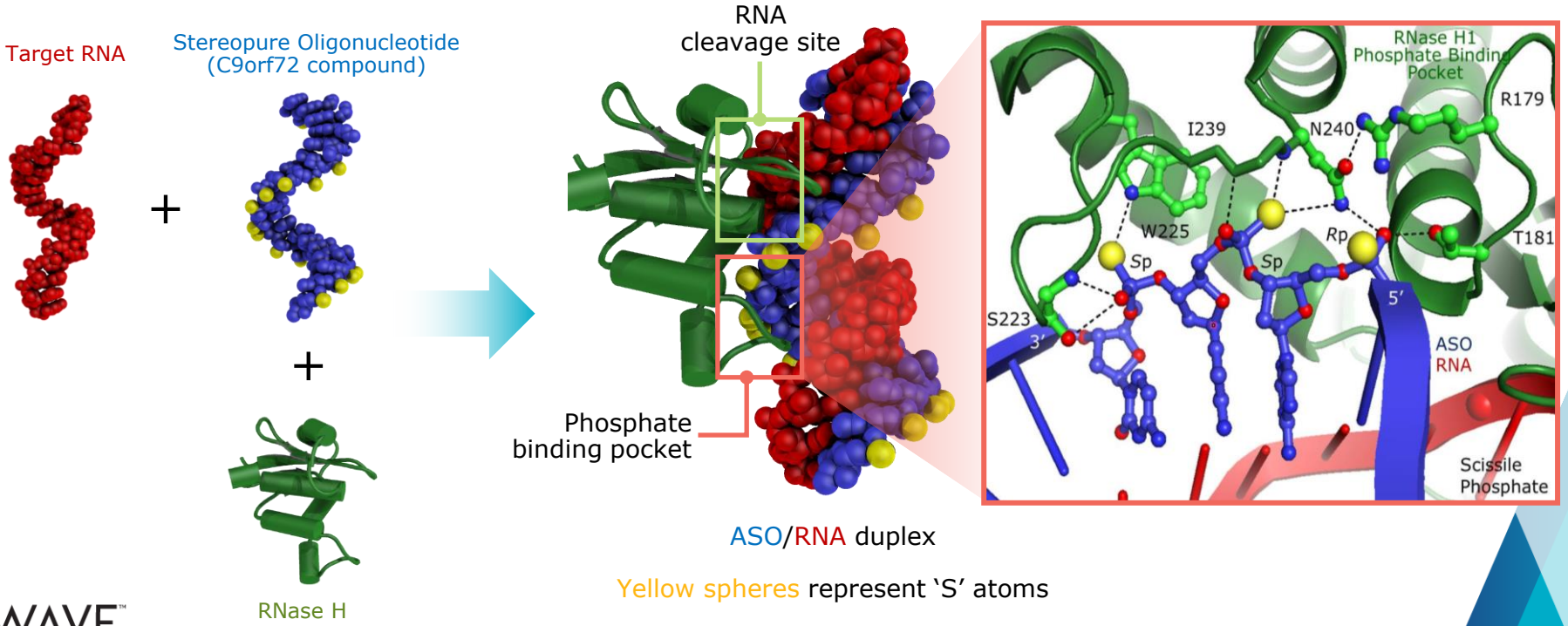
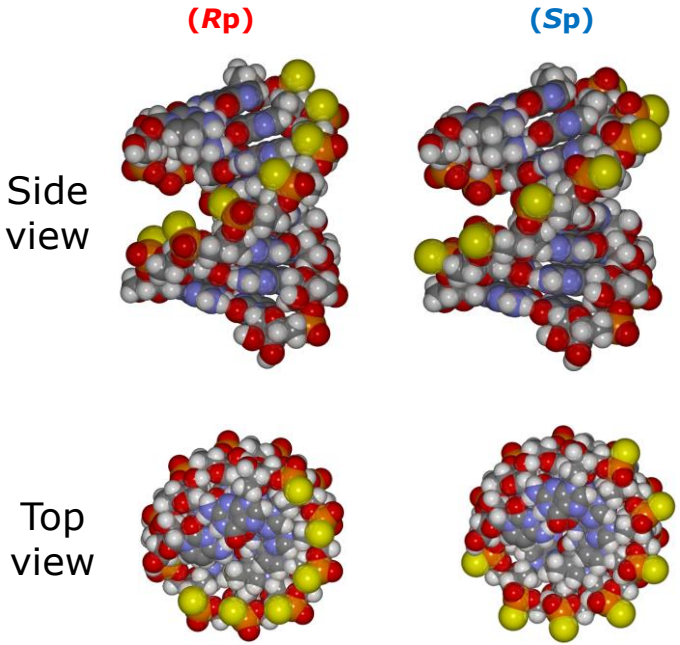
PRISM enables optimal placement of backbone stereochemistry

Crystal structure confirms phosphate-binding pocket of RNase H binds 3′-SSR-5′ motif in stereopure oligonucleotide – supports design strategy for Wave oligonucleotides

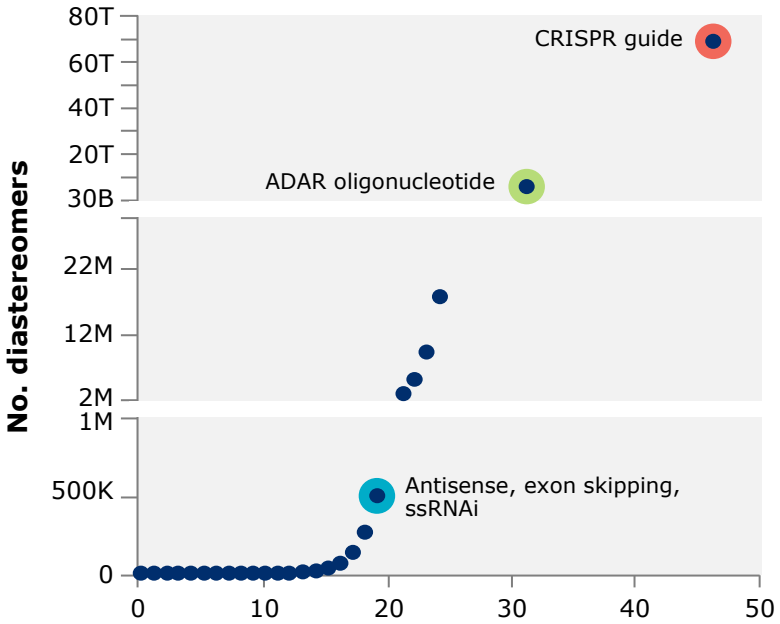


Importance of controlling stereochemistry

Stereochemical diversity



Exponential diversity arises from uncontrolled stereochemistry



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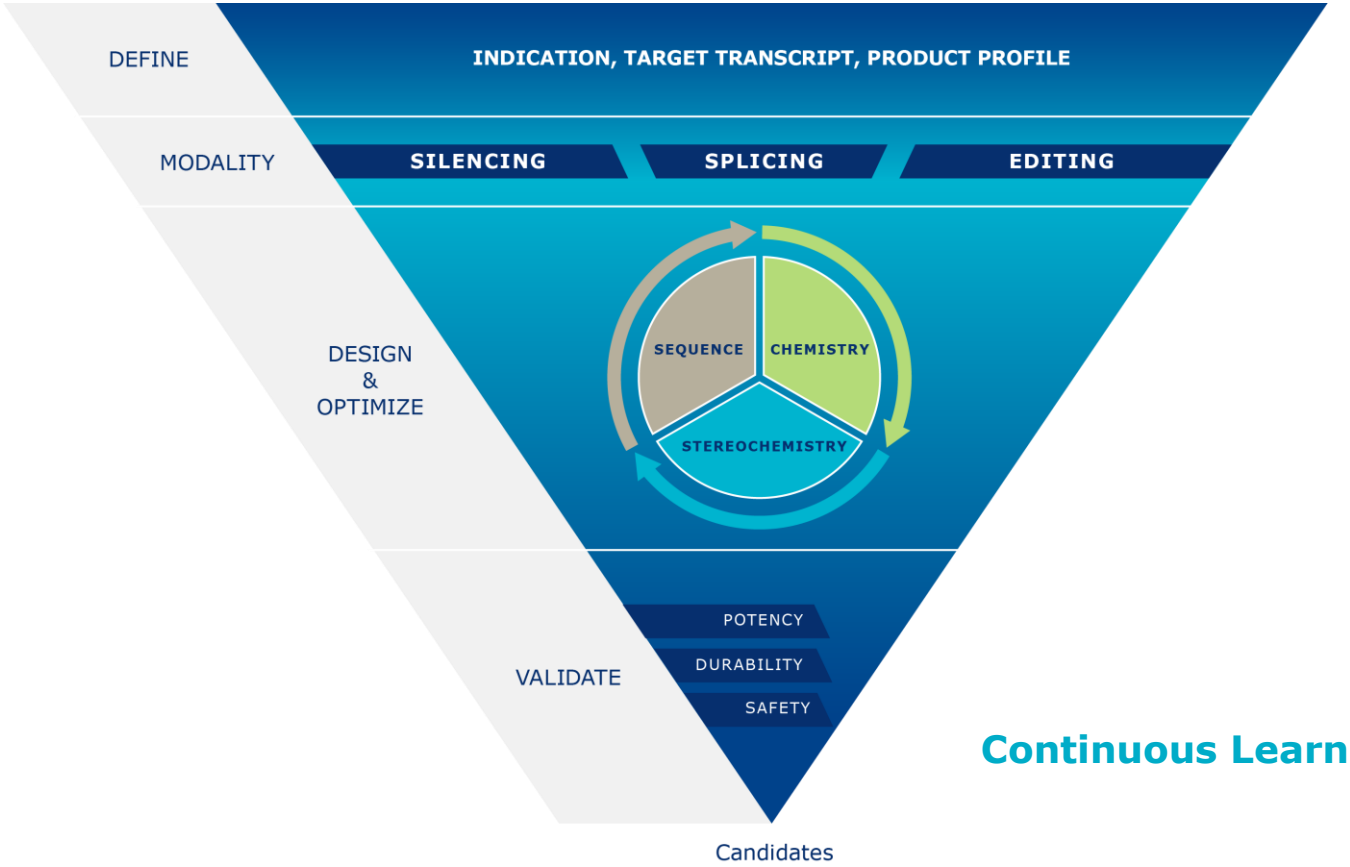
Yellow spheres represent 'S' atoms

PS: Phosphorothioate

PRISM platform enables rational drug design



Continuous Learning

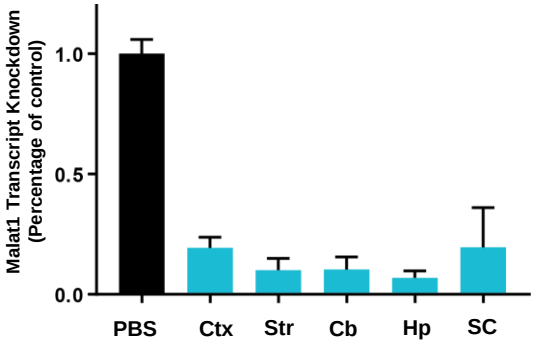
Source: Iwamoto N, et al. Control of phosphorothioate stereochemistry substantially increases the efficacy of antisense oligonucleotides. *Nat Biotechnol*. 2017;35:845-851.

Optimizing potency and durability across multiple tissues

CNS

Malat1 Transcript Knockdown in Mice

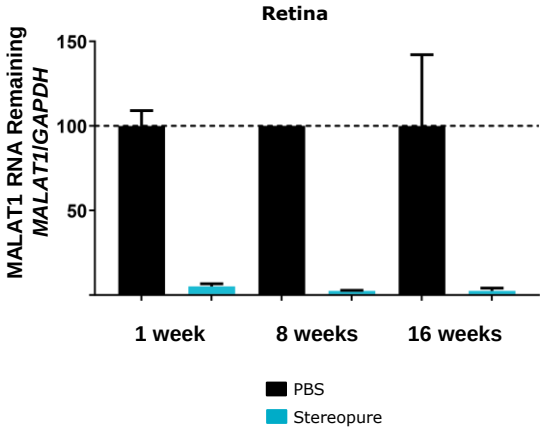
10 Weeks after single 100 µg ICV injection



Eye

MALAT1 Knockdown in Non-Human Primates

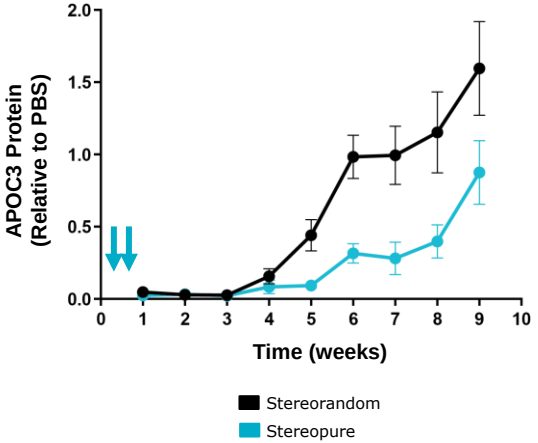
Single 450 µg IVT injection



Liver

Knockdown of Serum APOC3 Protein Levels in Mice

Two 5 mg/kg SC injections on Days 1&3



Data represented in this slide from *in vivo* studies. CNS: Central nervous system; PBS = phosphate buffered saline; Ctx = cortex; Str = striatum; Cb = cerebellum; Hp = hippocampus; SC = spinal cord. ICV = intracerebral; IVT = intravitreal; IV = intravenous; SC= subcutaneous.

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ADAR-mediated RNA editing

ADAR editing: A promising new therapeutic modality for treatment of genetic diseases

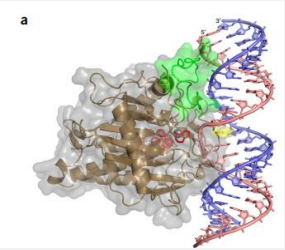
Potential benefits versus gene editing

- Ability to use endogenous proteins (e.g. ADAR)
- Ease of delivery
- Titratable, repeatable dosing
- Reversible effects, avoids potential long-term risks associated with permanent off-target DNA editing

A-to-I(G) RNA editing opportunity is significant

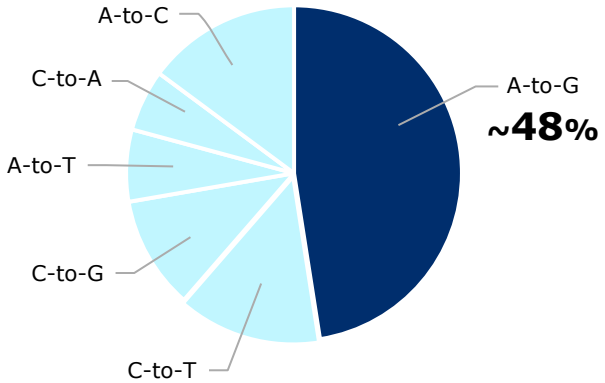
- Nearly half of known human genetic pathogenic SNPs are G-to-A mutations[1]
- Tens of thousands of potential disease variants A-to-I(G) editing could target[2]

ADAR
(adenosine deaminases acting on RNA)



- Endogenous proteins that catalyze A-to-I RNA editing
- Upon translation, I recognized as G, leading to A-to-G editing

Pathogenic human SNPs by base pair corrections

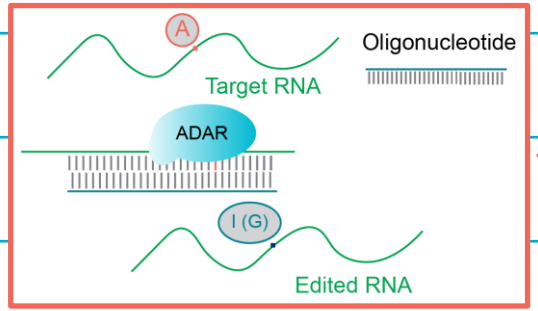


>32,000 pathogenic human SNPs[1]

SNP: single nucleotide polymorphism A: Adenosine I: Inosine G: Guanosine
[1] Gaudeli NM et al. *Nature* (2017). [2] ClinVar database

ADAR editing can be used for several therapeutic applications and supplement Wave's existing modalities

Strategy	Therapeutic Application	Treatment Modality: Silencing	Splicing	ADAR Editing
Silence protein expression	Reduce levels of toxic mRNA/protein	✓		✓
Alter mRNA splicing	Exon skipping/inclusion/ restore frame		✓	✓
Fix nonsense mutations that cannot be splice-corrected	Restore protein expression			✓
Fix missense mutations that cannot be splice-corrected	Restore protein function			✓
Modify amino acid codons	Alter protein function			✓
Remove upstream ORF	Increase protein expression			✓



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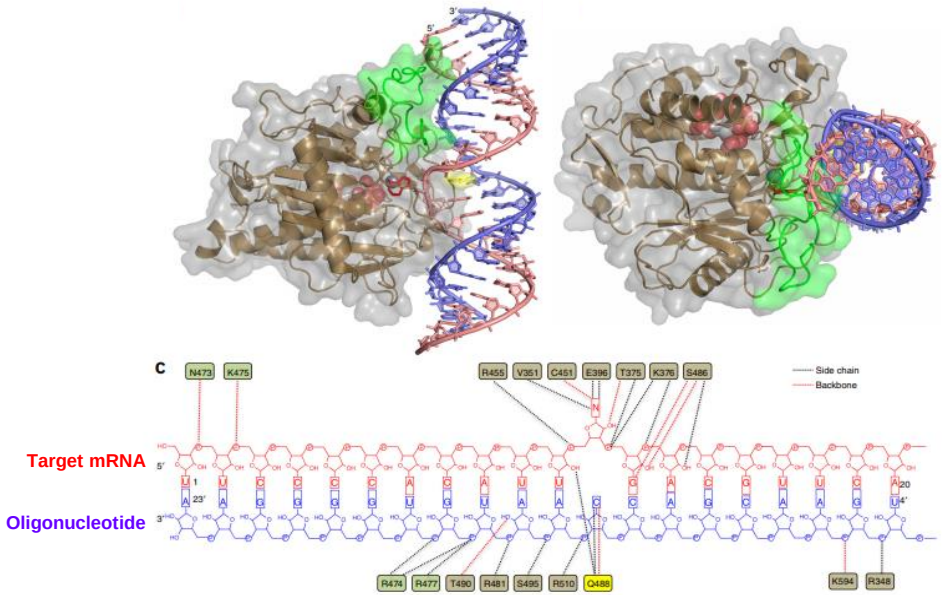
I (G): ADAR converts A>I, I is recognized as G by all cellular machinery; ADAR: Adenosine Deaminase Acting on RNA; ORF: Open reading frame

Using PRISM to unlock ADAR-mediated RNA editing

Structure of ADAR deaminase domain bound to dsRNA substrate

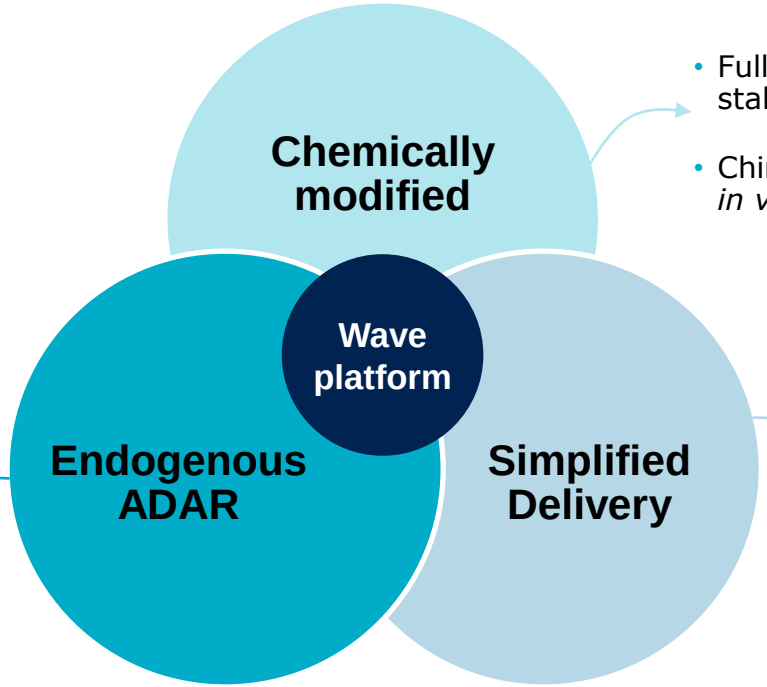


- ADAR makes multiple contacts with oligonucleotide backbone, sugar and bases
- Using PRISM platform, rationally designed and screened oligonucleotides to optimize:
  - 2' sugar chemistry
  - Backbone chemistry and stereochemistry
  - Size and structure
  - Modified nucleobases

~1,000 RNA editing oligonucleotides tested over the last year to develop SAR for editing format

Structure adapted from Matthews et al., Nat Struct Mol Biol. (2016); SAR = structure-activity relationship; ADAR: Adenosine Deaminase Acting on RNA; dsRNA = double-stranded RNA

Advantages of Wave ADAR-mediated RNA-editing platform



- Fully chemically modified to increase stability *in vivo*
- Chirally-controlled backbone to maximize *in vitro* activity

- No immunogenicity from exogenous proteins
- Reduced off-target effects[1]

- GalNAc-conjugated for targeted delivery into liver
- No requirement for AAV / nanoparticles

Building RNA-editing capability for PRISM platform

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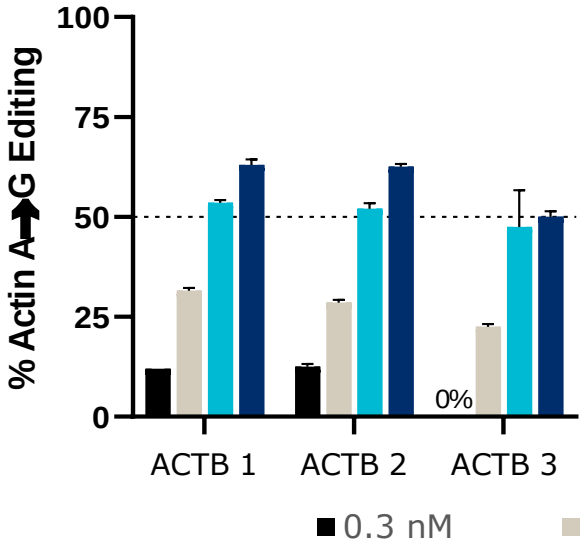
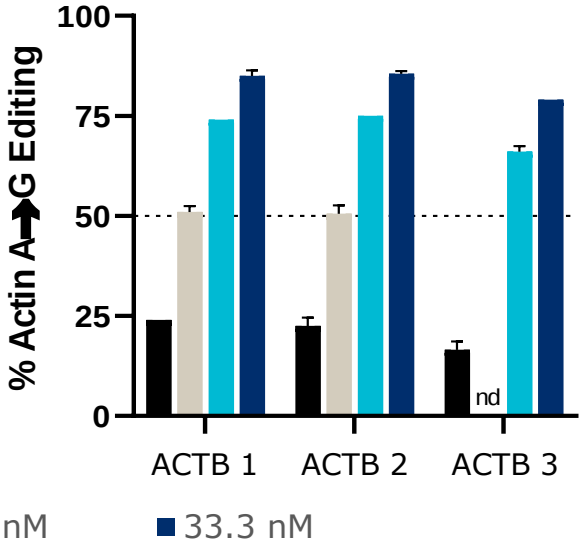
[1]Chen et al. Biochemistry 2019

In vitro RNA editing demonstrated in non-human primate and human hepatocytes

NHP Hepatocytes



Human Hepatocytes

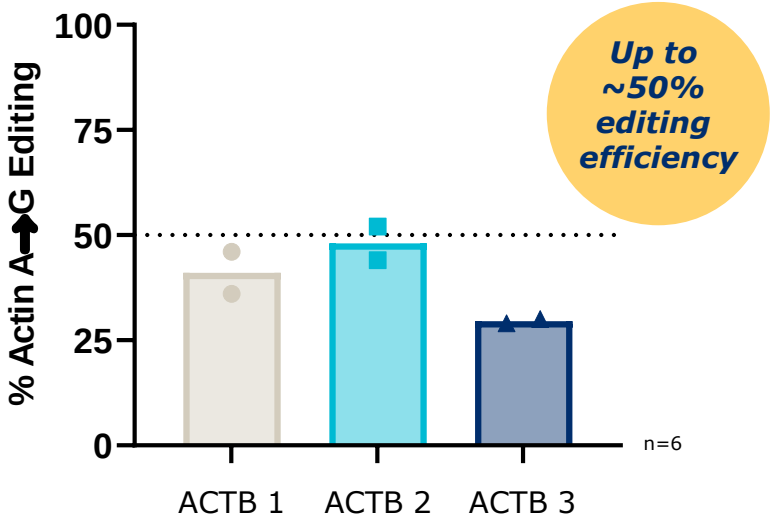


Potent, dose-dependent RNA editing demonstrated via free uptake with GalNAc-conjugated stereopure oligonucleotides

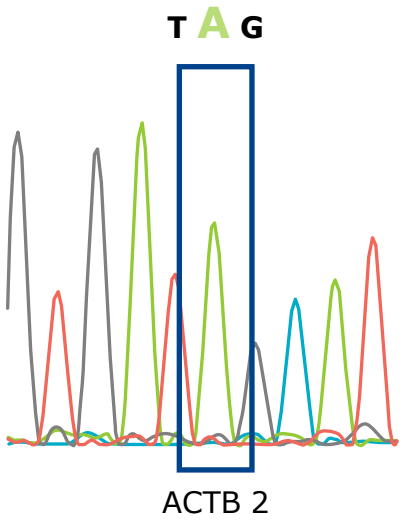
NHP: non-human primate; ACTB: Beta-actin; nd= not determined
Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR.

First non-human primate RNA editing

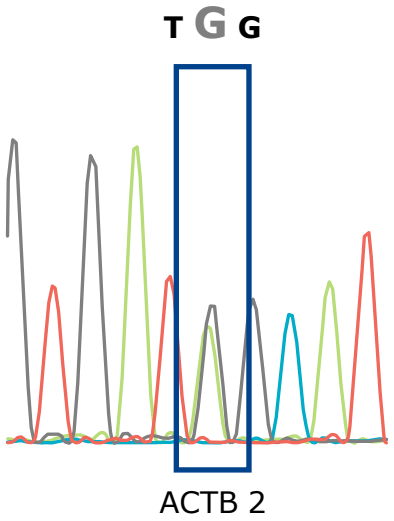
In vivo – NHP



Baseline



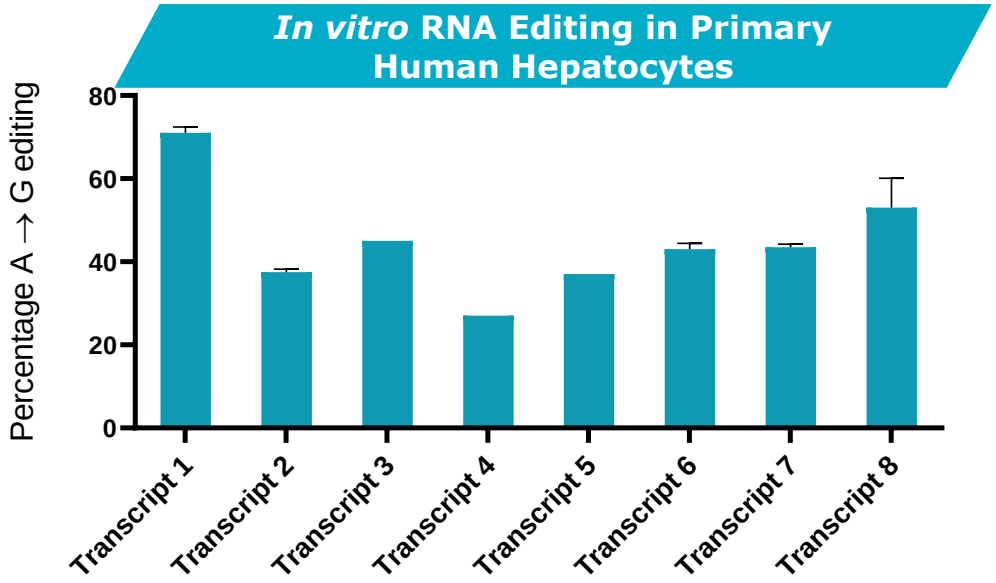
Post-treatment



Liver biopsies conducted at baseline and 2 days post last dose
RNA-editing efficiencies of up to 50% with GalNAc conjugate in liver of NHP

NHP – non-human primate; ACTB: Beta-actin; Left: 5mg/kg SC: Day 1,2,3,4,5; Liver Biopsy for mRNA (ACTB Editing) & eASO Exposure: Day 7 Right: % Editing quantified from Sanger sequencing using EditR program.

RNA-editing design applicable across targets



- Editing achieved across several distinct RNA transcripts
- Supports potential for technology to be applied across variety of disease targets

Additional *in vivo* ADAR-mediated RNA-editing data and first ADAR editing program expected to be announced in 2020

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Data presented at 1st International Conference on Base Editing – Enzymes and Applications (Deaminet 2020); See poster for full dataset

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Ophthalmology

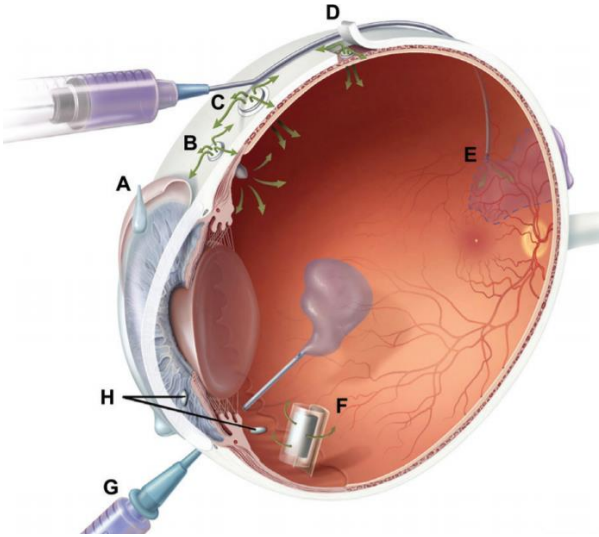
Stereopure oligonucleotides for inherited retinal diseases (IRDs)

Wave ophthalmology opportunity

- Oligonucleotides can be administered by intravitreal (IVT) injection; targeting twice per year dosing
- Stereopure oligonucleotides open novel strategies in both dominant and recessive IRDs; potential for potent and durable effect with low immune response

Successful targeting of *MALAT1* is a surrogate for an ASO mechanism of action

- Widely expressed in many different cell types
- Only expressed in the nucleus



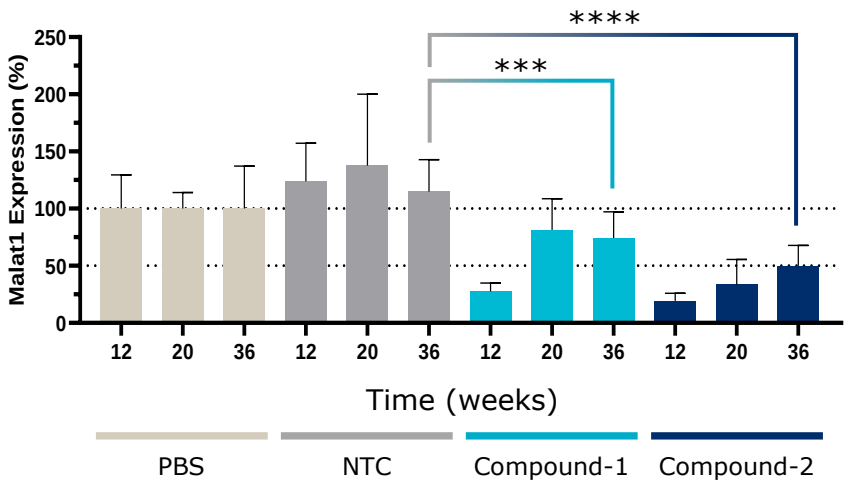
Intravitreal injection

Sources: Daiger S, et al. *Clin Genet*. 2013;84:132-141. Wong CH, et al. *Biostatistics*. 2018; DOI: 10.1093/biostatistics/kxx069. Athanasiou D, et al. *Prog Retin Eye Res*. 2018;62:1–23. Daiger S, et al. *Cold Spring Harb Perspect Med*. 2015;5:a017129. Verbakel S, et al. *Prog Retin Eye Res*. 2018:66:157-186.; Short, B.G.; *Toxicology Pathology*, Jan 2008.

Stereopure compound induces potent and durable *MALAT1* knockdown in the eye

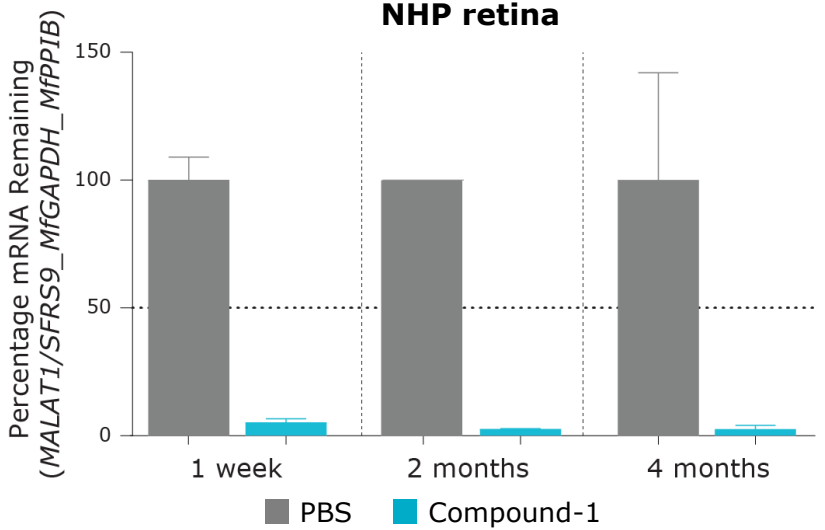
~50% *MALAT1* knockdown at 9 months

In vivo duration of effect in the mouse retina



>90% knockdown of *MALAT1* maintained for 4 months

In vivo duration of effect in the NHP retina



Mouse: Compound or PBS (1 x 50 mg IVT) was delivered to C57BL6 mice. Relative percentage of Malat1 RNA in the posterior of the eye (retina, choroid, sclera) to PBS-treated mice is shown at 12, 20 and 36 weeks post-single injection. Statistics: Compound-2 Malat1 levels are significantly different from NTC at 36 weeks ***, P<0.001; **** P<0.0001, respectively. PBS = phosphate buffered saline; NTC= chemistry matched non-targeting control; Compound-1 and Compound-2 are stereopure MALAT1-targeting antisense oligonucleotide. NHP: Oligonucleotide or PBS (1 x 450 μg IVT) was delivered to NHP. Relative percentage of *MALAT1* RNA in the retina to PBS-treated is shown at 1 week, 2 and 4 months, post-single injection. Compound-1 is a stereopure *MALAT1*-RNA-targeting antisense oligonucleotide.

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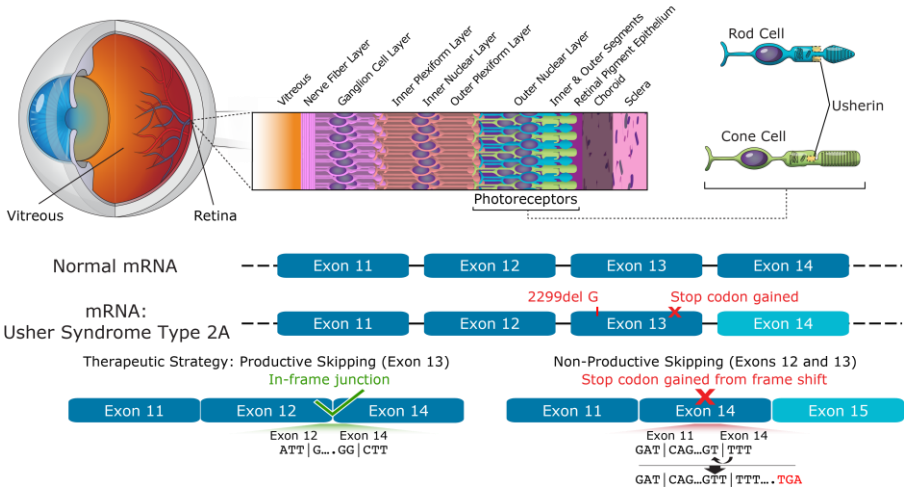
Usher Syndrome Type 2A: a progressive vision loss disorder

- Autosomal recessive disease characterized by hearing loss at birth and progressive vision loss beginning in adolescence or adulthood
- Caused by mutations in USH2A gene (72 exons) that disrupt production of usherin protein in retina, leading to degeneration of the photoreceptors
- No approved disease-modifying therapies
- **~5,000 addressable patients in US**



Oligonucleotides that promote USH2A exon 13 skipping may restore production of functional usherin protein

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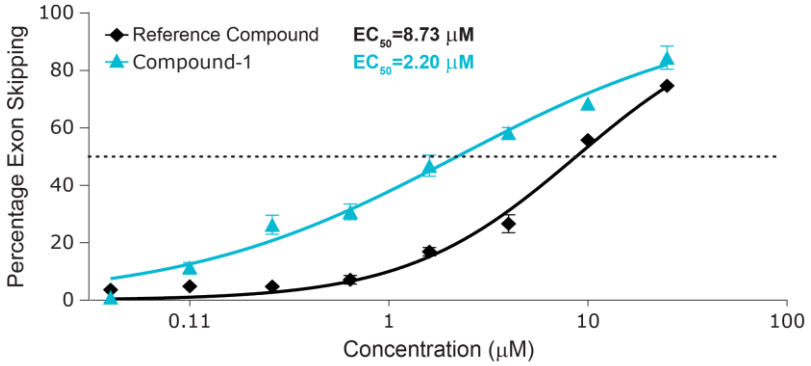
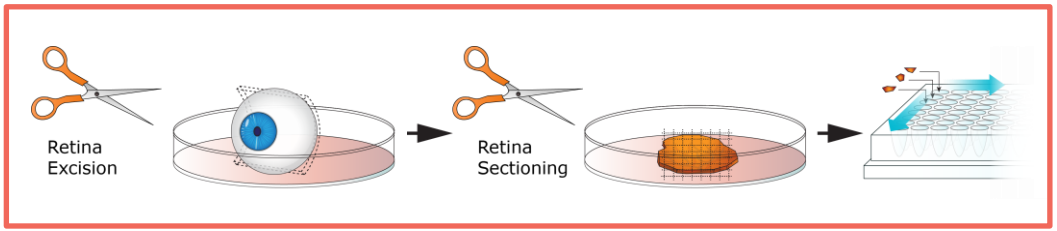
Sources: Boughman et al., 1983. *J Chron Dis*. 36:595-603; Seyedahmadi et al., 2004. *Exp Eye Res.* 79:167-173; Liu et al., 2007. *Proc Natl Acad Sci USA* 104:4413-4418.

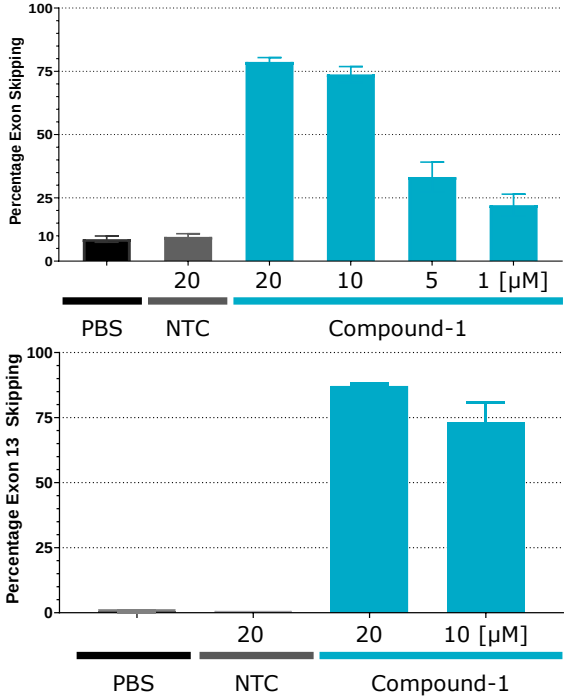
Potent USH2A exon 13 skipping with stereopure compound in *vitro* and *ex vivo*

Enhanced potency over a stereorandom reference compound (*in vitro*)





Target engagement in NHP and human retinas (*ex vivo*)

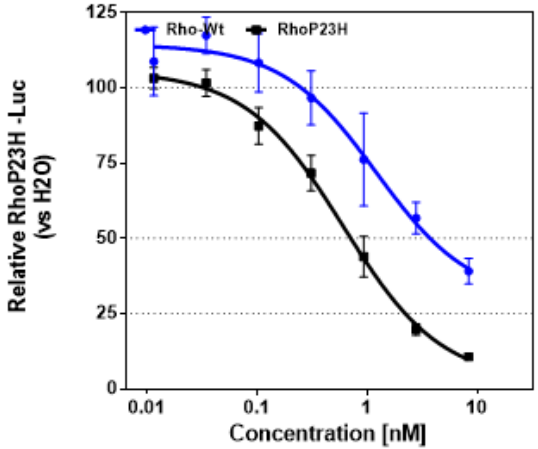


Left: Compounds were added to Y79 cells under free-uptake conditions. Exon skipping was evaluated by Taqman assays. *USH2A* transcripts were normalized to *SRSF9*. Data are mean±s.d., n=2. Reference Compound: van Diepen *et al.* 2018. Antisense oligonucleotides for the treatment of eye disease. W02018055134A1. Compound-1 is a stereopure antisense oligonucleotide. Right: Whole NHP and human eyes were enucleated (n=4 and n=2, respectively) and compounds (1–20 µM) were added to extracted retinas under free-uptake conditions. Exon skipping was evaluated by 48 hrs later by Taqman assays on RNA. USH2A transcript levels were normalized to SRSF9. Data presented are mean± s.e.m.

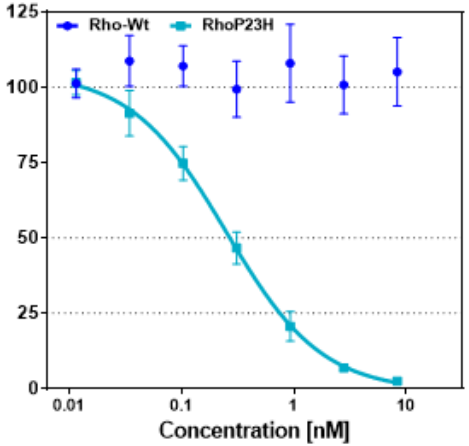
Allele-selective reduction of SNP-containing allele for adRP associated with Rhodopsin P23H mutation

- **Retinitis pigmentosa (RP)**: group of rare, genetic eye disorders resulting in progressive photoreceptor cell death and gradual functional loss; currently no cure
- ~10% of US autosomal dominant RP cases are caused by the P23H mutation in the rhodopsin gene (RHO)
- 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

Stereorandom



Stereopure



In vivo

Collaborations in place for evaluation in transgenic human Rho P23H pig model

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Ferrari et al., *Current Genomics.* 2011;12:238-249.; 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.

Anticipated upcoming Wave milestones

NEUROLOGY

Huntington's disease

- **4Q 2020**: Initiate clinical development with CTA filing of SNP3 program
- **1Q 2021**: PRECISION-HD2 data from 32 mg cohort and data from OLE trial
- **1Q 2021**: PRECISION-HD1 data, including 32 mg cohort, and data from OLE trial

ALS and FTD

- **4Q 2020**: Initiate clinical development with CTA filing of C9orf72 program in ALS and FTD

PRISM

ADAR editing

- ✓ *In vivo* ADAR-mediated RNA editing data
  - **August 2020**: Additional *in vivo* ADAR editing data at Research webcast
  - **2020**: Announce first ADAR editing program

PRISM platform updates in 2020

- Research webcast to be held August 25

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ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; CTA: clinical trial application; OLE: open-label extension

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Realizing a brighter future for people affected by genetic diseases

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