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Wave Life Sciences

Jefferies Virtual Healthcare Conference

June 4, 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
- Alzheimer’s

PRISM™

Silencing | Skipping | Editing

CLINICAL DEVELOPMENT EXPERTISE

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

MANUFACTURING

- Established internal manufacturing capabilities to produce oligonucleotides at scale

Innovative pipeline led by neurology programs

THERAPEUTIC AREA	TARGET	DISCOVERY	PRECLINICAL	CLINICAL	ESTIMATED U.S. PREVALENCE*	PARTNER
NEUROLOGY						
Huntington's disease	**WVE-120101** mHTT SNP1			Phase 1b/2a and OLE	~10,000 / ~35,000	Takeda 50:50 option
	WVE-120102 mHTT SNP2			Phase 1b/2a and OLE	~10,000 / ~35,000	Takeda 50:50 option
	mHTT SNP3				~8,000 / ~30,000	Takeda 50:50 option
ALS and FTD	C9orf72				~1,800 (ALS) ~7,000 (FTD)	Takeda 50:50 option
Spinocerebellar ataxia 3	ATXN3				~4,500	Takeda 50:50 option
CNS diseases	Multiple†					Takeda milestones & royalties
OPHTHALMOLOGY						
Retinal diseases	USH2A and RhoP23H					100% global
HEPATIC						
ADAR RNA-editing	Multiple					100% global

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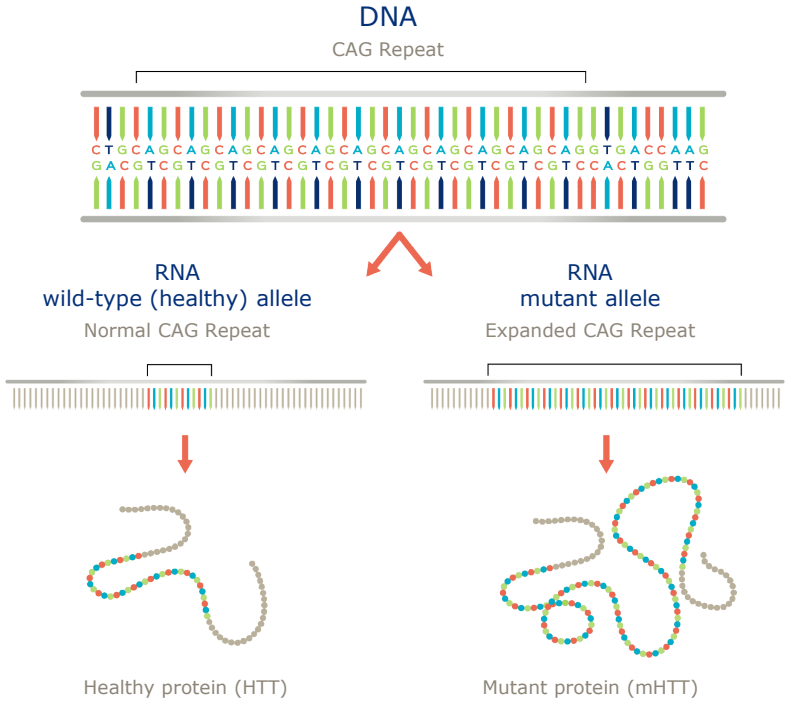
*Estimates of U.S. prevalence and addressable population by target based on publicly available data and are approximate; for Huntington's disease, numbers approximate manifest and pre-manifest populations, respectively.
†During a four-year term, Wave and Takeda may collaborate on up to six preclinical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

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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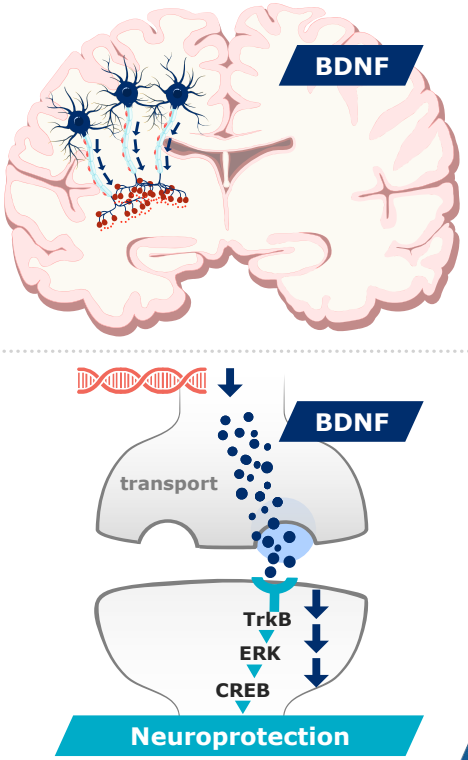
Importance of wild-type huntingtin (wtHTT) in HD

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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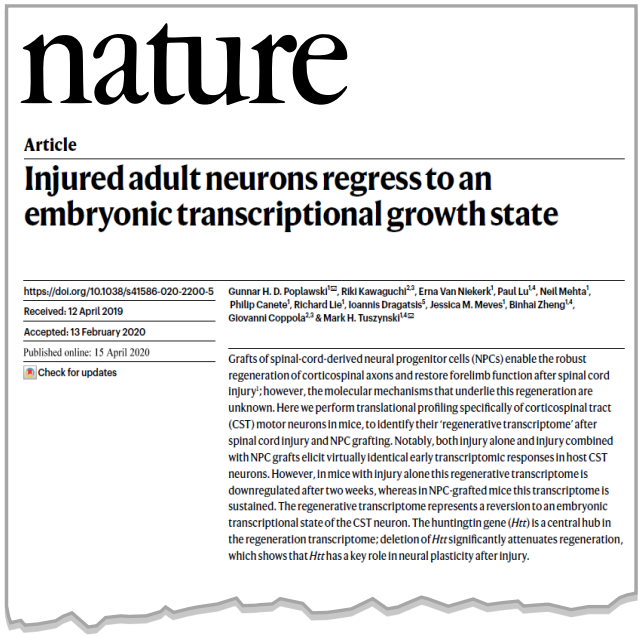
Sources: Van Raamsdonk, J.M., et al., Hum Mol Genet, 2005; Van Raamsdonk, J.M., et al., BMC Neurosci, 2006; Becanovic, K., et al., Nat Neurosci, 2015; Saudou, F. and S. Humbert, The Biology of Huntingtin. Neuron, 2016; Gauthier, L.R., et al., Cell, 2004; Caviston, J.P. and E.L. Holzbaur, Trends Cell 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

Recent 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
Received: 12 April 2019
Accepted: 13 February 2020
Published online: 15 April 2020
Check for updates

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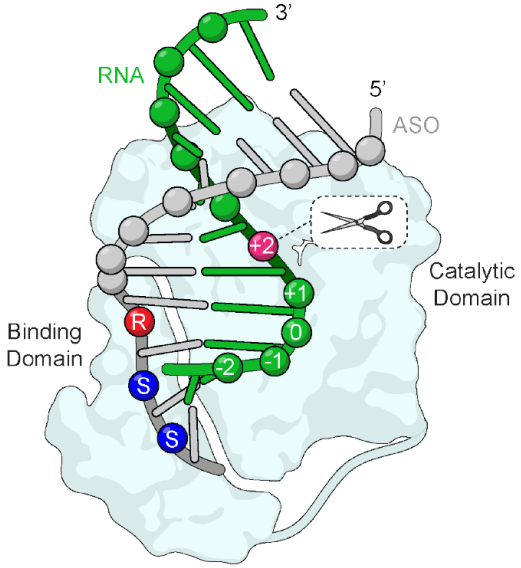
Poplawski et al., *Nature*, April 2019; Htt: Huntingtin protein

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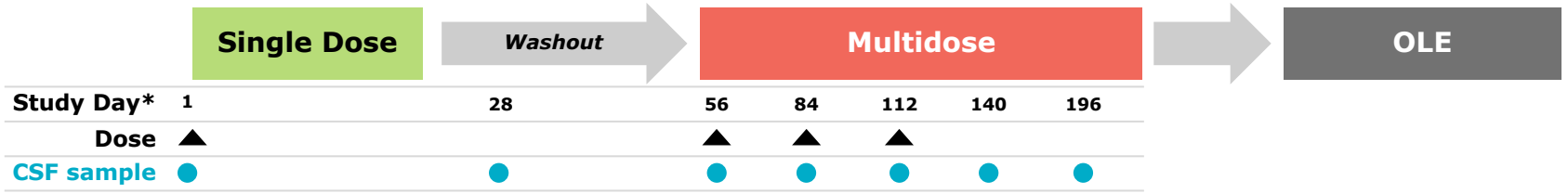
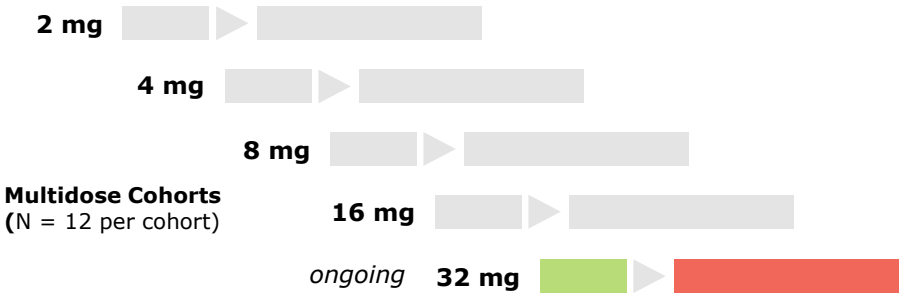
Source: Kay, et al. Personalized gene silencing therapeutics for Huntington disease. *Clin Genet.* 2014;86:29–36.

PRECISION-HD clinical trials

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





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

- Not all patients had reached Day 140 at interim analysis
- **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]
- Potential for greater mHTT reduction at higher doses
- **No change in total HTT**; Larger reductions of mHTT expected to result in discernible impact on tHTT

PRECISION-HD2 and PRECISION-HD1 data, including 32 mg cohorts, expected in 2H 2020

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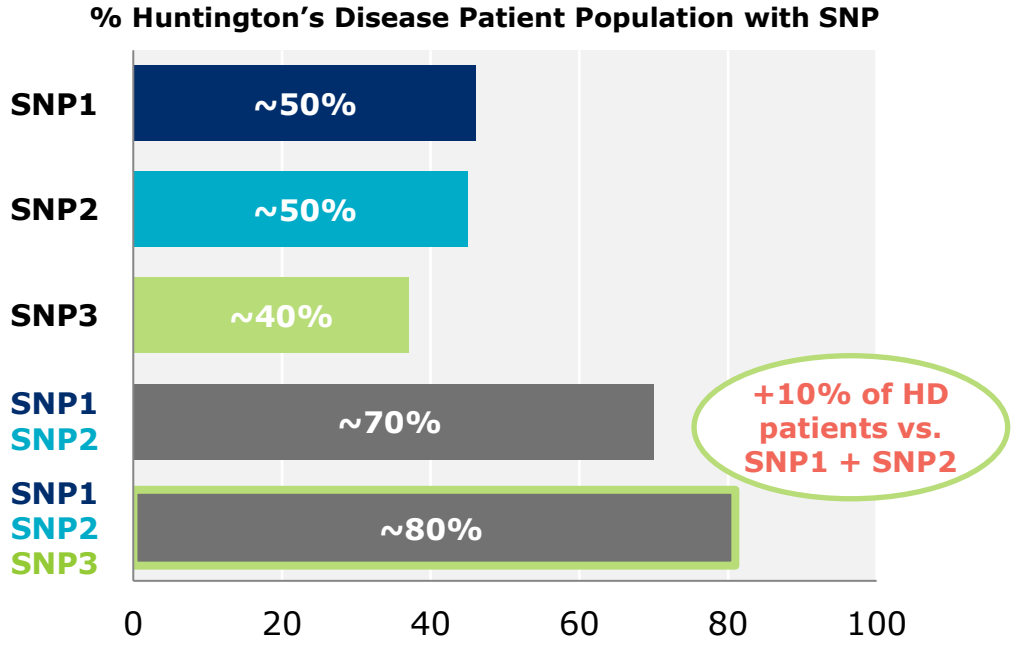
OLE: Open label extension; CSF: cerebrospinal fluid; mHTT: mutant huntingtin; wtHTT: wild-type HTT; tHTT: total HTT
* Study day may vary depending on patient washout period [1]Hodges-Lehmann non-parametric shift estimates of the difference between treatment and placebo, p<0.05 (Wilcoxon-Mann-Whitney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

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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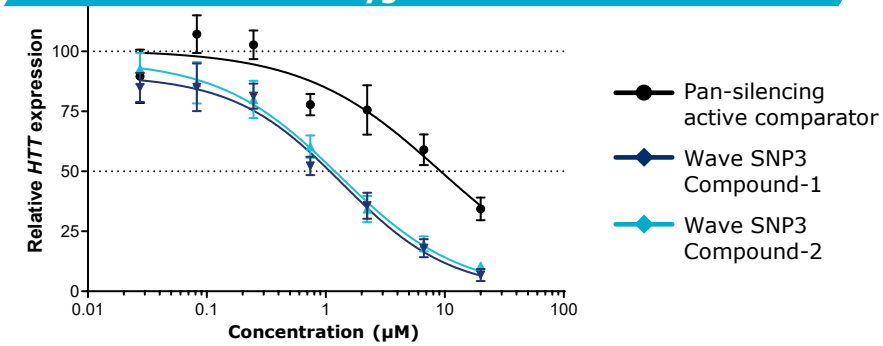
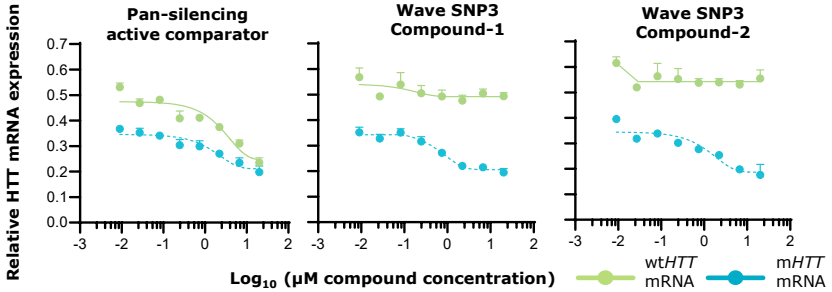
SNP3 program approaching clinical development

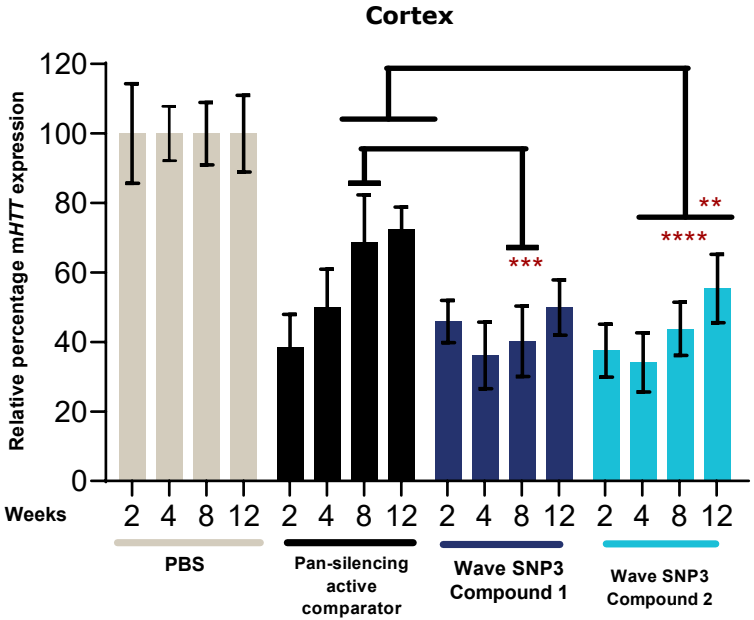
Potent mutant *HTT* knockdown activity in homozygous iCell neurons



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 in 2H 2020

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

[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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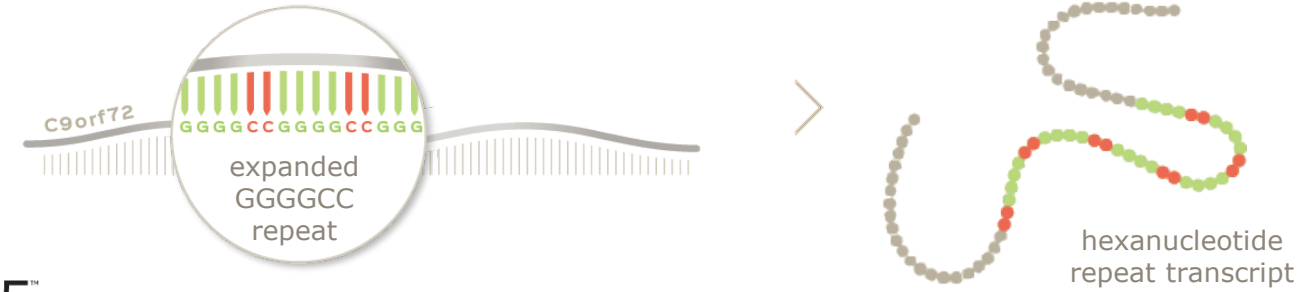
C9orf72: a critical genetic risk factor

- 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 dipeptide repeat proteins that accumulate in brain 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
- Availability of dipeptide biomarker in CSF has potential to accelerate drug development



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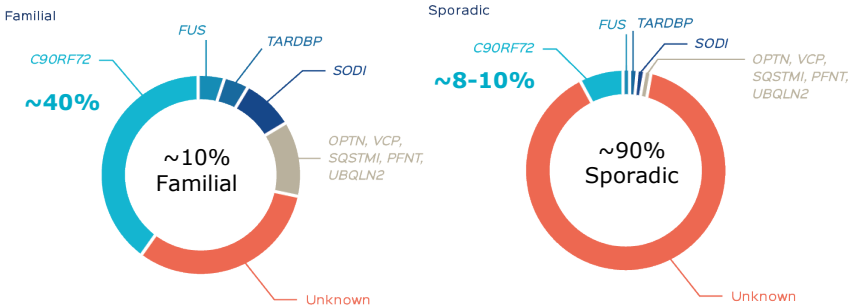
Source: DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. *Neuron.* 2011;72:245-256. Renton AE, Majounie E, Waite A, et al. *Neuron.* 2011;72:257-268.

Targeting patients with C9orf72 genetic mutations

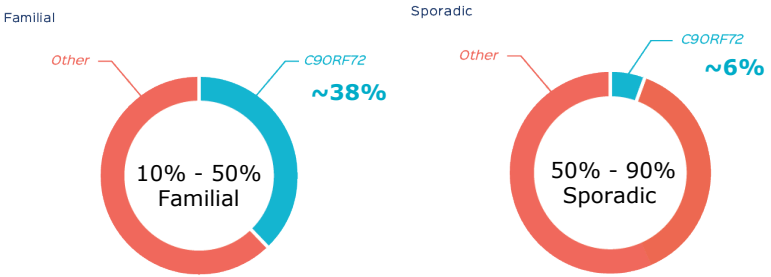
Amyotrophic lateral sclerosis (ALS)

- 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.

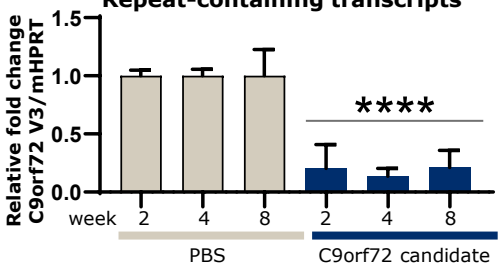
C9orf72 program: Selective silencing *in vivo* of expanded C9orf72 repeat transcripts

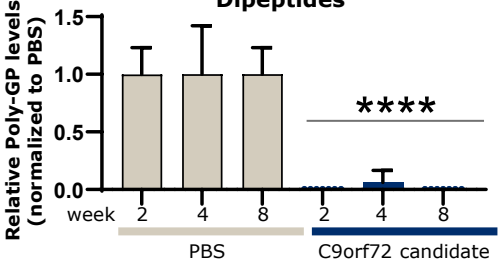
- C9orf72 genetic mutations are the most common cause of familial Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) and are the strongest genetic risk factor found to date for the more common, non-inherited (sporadic) forms of ALS and FTD; Hexanucleotide repeat drives the formation and accumulation of dipeptide repeat proteins that accumulate in brain tissue
- **Wave's approach:** Selectively silence the repeat containing transcript while minimizing the impact on C9orf72 protein

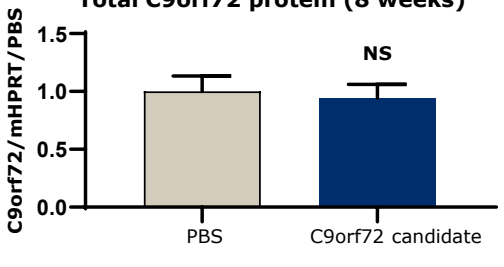
Potent *in vivo* knockdown of repeat containing transcripts and dipeptides

Protein preservation

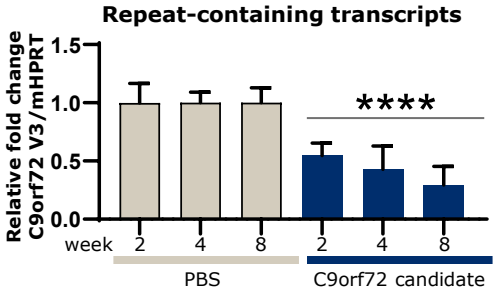
Spinal Cord

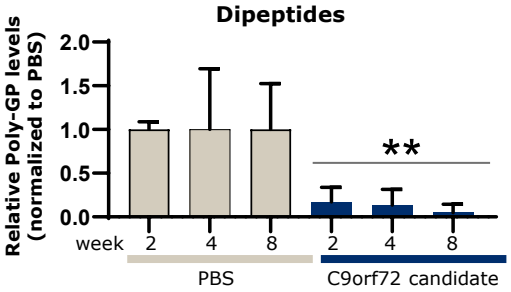


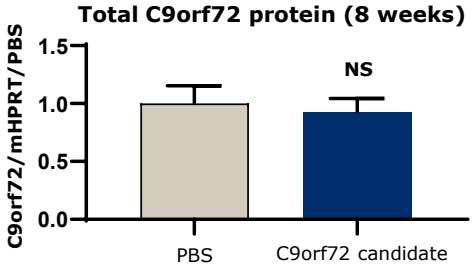




Cortex







Clinical development expected to initiate in 2H 2020

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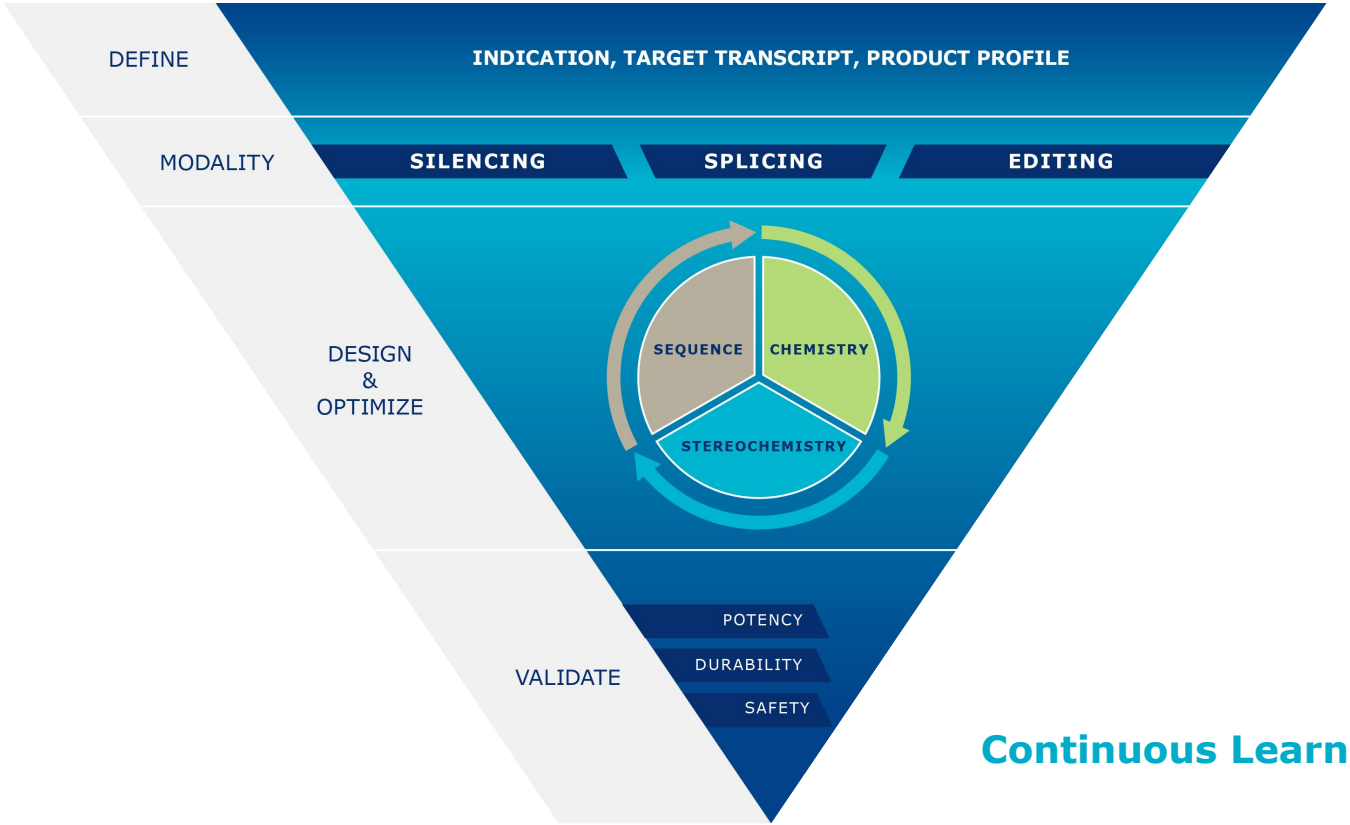
Experimental description: 2 x 50 ug on day 1 and day 8; mRNA Samples were analyzed using quantitative PCR (Taqman assay), Protein samples were measured by Western Blot. Dipeptide repeat proteins were measured by Poly-GP MSD assay.

PRISM platform enables rational drug design



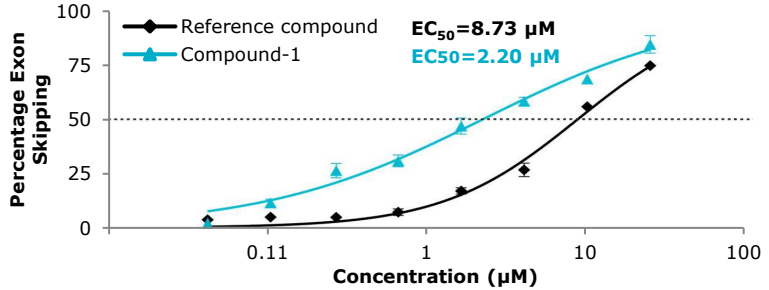
Continuous Learning

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

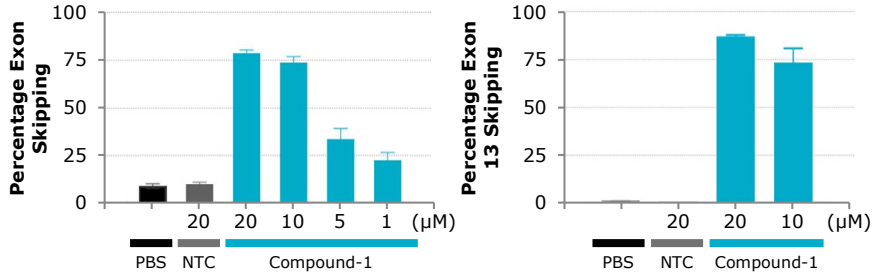
Ophthalmology: USH2A and RhoP23H

USH2A

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



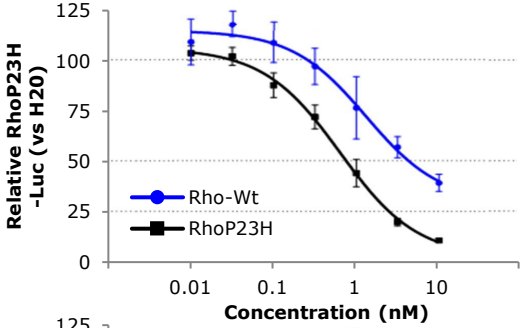
Target engagement in NHP (left) and human retinas (right) *ex vivo*



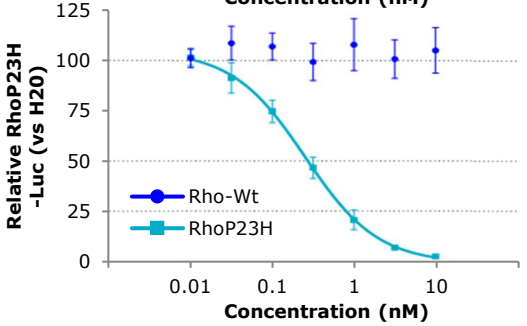
RhoP23H

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

Stereorandom
(Reference compound)



Stereopure



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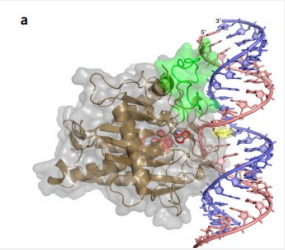
USH2A: Data presented at 15th Annual Meeting of the Oligonucleotide Therapeutics Society, October 2019; See poster for full dataset
RhoP23H: Reporter assays on a Wave stereopure sequence as well as a sequence described in WO2016138353A1: ASO and luciferase reporter plasmids (wild-type and mutant rhodopsin) are transfected into Cos7 cells. 48-hours later, cells are harvested, and relative luminescence is measured.

RNA 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

ADAR
(adenosine deaminases acting on RNA)

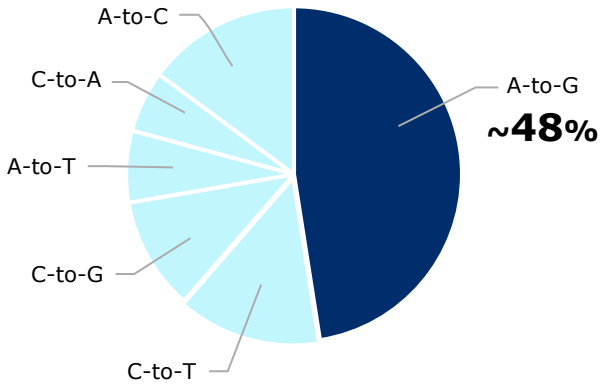


- Endogenous proteins that catalyze A-to-I RNA editing
- Upon translation, I recognized as G, leading to A-to-G editing

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]

Pathogenic human SNPs by base pair corrections

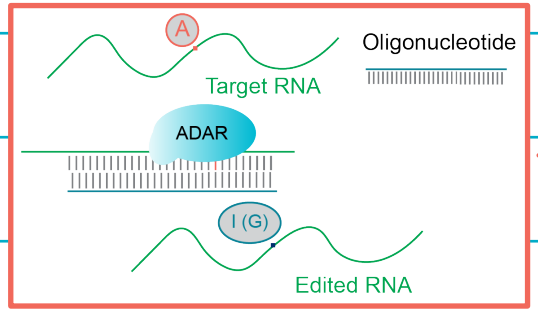


>32,000 pathogenic human SNPs[1]

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

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

Strategy	Therapeutic Application	Treatment Modality: Silencing	Splicing	RNA 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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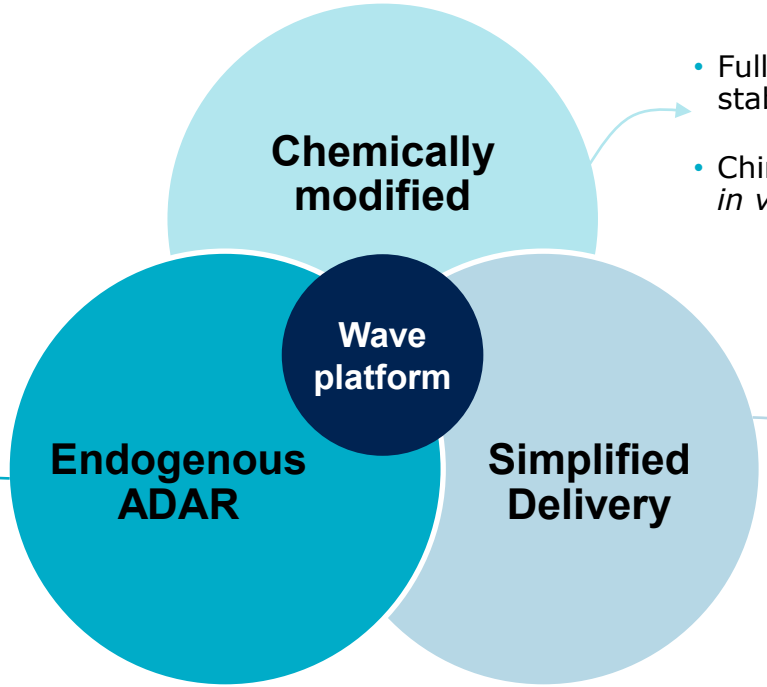
I (G): ADAR converts A>I, I is recognized as G by all cellular machinery; ADAR: Adenosine Deaminase Acting on RNA; ORF: Open reading frame

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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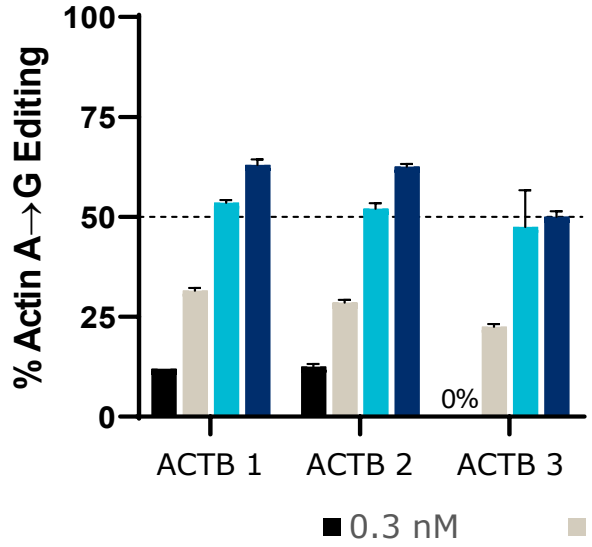
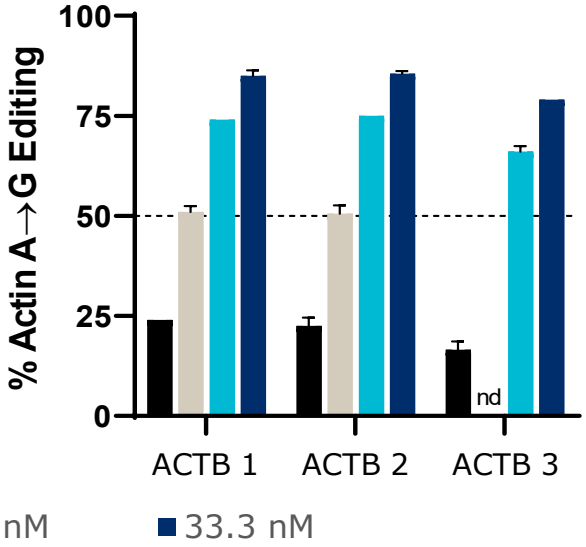
[1]Chen et al. Biochemistry 2019

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

NHP Hepatocytes



Human Hepatocytes



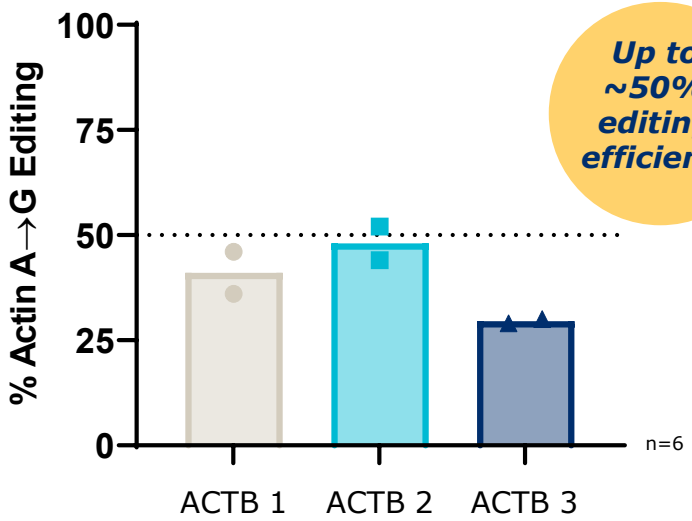
0.3 nM 1.3 nM 6.7 nM 33.3 nM

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

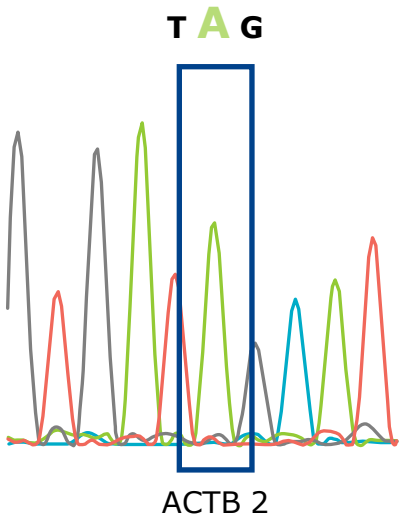
NHP: non-human primate; ACTB: Beta-actin; nd= not determined
Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR.

First non-human primate RNA editing

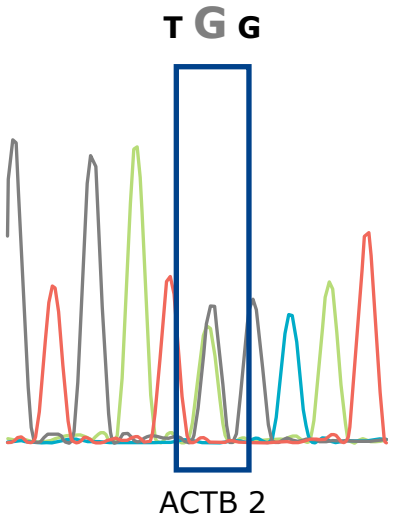
In vivo – NHP



Baseline



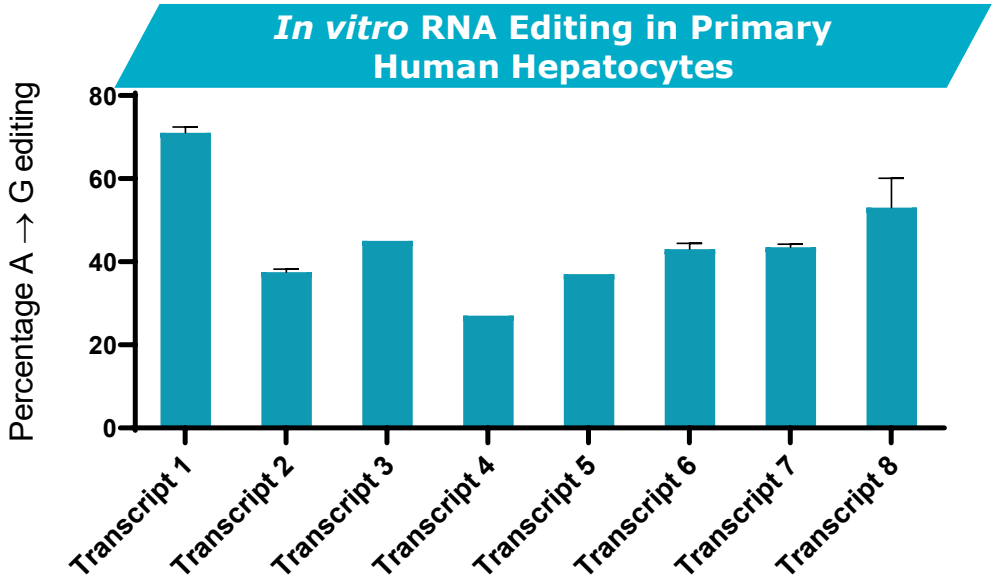
Post-treatment



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 RNA-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

Anticipated upcoming Wave milestones

NEUROLOGY

Two data readouts in Huntington's disease in 2H 2020

- PRECISION-HD2 data from 32 mg cohort in Huntington's disease
- PRECISION-HD1 topline data, including 32 mg cohort, in Huntington's disease

Two CTA submissions in 2H 2020

- Initiate clinical development of C9orf72 program in ALS and FTD
- Initiate clinical development of SNP3 program in Huntington's disease

PRISM

RNA-editing data in 2020

- ✓ *In vivo* ADAR editing data
- Additional *in vivo* ADAR-mediated RNA-editing data and announce first RNA-editing program

PRISM platform updates in 2020

- Provide updates on platform evolution

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