UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): December 16, 2019

WAVE LIFE SCIENCES LTD.
(Exact name of registrant as specified in its charter)

Singapore	**001-37627**	**Not applicable**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

7 Straits View #12-00, Marina One East Tower	
Singapore	**018936**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: +65 6236 3388

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading symbol	Name of each exchange on which registered
$0 Par Value Ordinary Shares	**WVE**	**The Nasdaq Global Market**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On December 16, 2019, Wave Life Sciences Ltd. (the "Company" or "Wave") issued a press release announcing the results of the interim analysis of the Open Label Extension phase of its Phase 1 clinical trial of investigational suvodirsen (WVE-210201) in boys with Duchenne muscular dystrophy (DMD) who are amenable to exon 51 skipping; and the discontinuation of the Company's suvodirsen development program. In addition, the press release indicated that Wave management will host an investor conference call at 8:00 a.m. ET on December 16, 2019 to discuss the results. A copy of the press release is attached hereto as Exhibit 99.1 and is incorporated by reference herein.

From time to time, the Company presents and/or distributes slides and presentations to the investment community to provide updates and summaries of its business. In connection with the announcement described above, on December 16, 2019, the Company updated its corporate presentation, which is available on the "For Investors & Media" section of the Company's website at http://ir.wavelifesciences.com/. This presentation is also furnished as Exhibit 99.2 to this Current Report on Form 8-K and is incorporated by reference herein.

The information in this Item 7.01 shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 8.01 Other Events.

The information set forth in the press release dated December 16, 2019, other than the third, fifth and sixth paragraphs thereof, is incorporated by reference into this Item 8.01 of this Current Report on Form 8-K.

ITEM 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Press Release issued by Wave Life Sciences Ltd. dated December 16, 2019
99.2	Corporate Presentation of Wave Life Sciences Ltd. dated December 16, 2019
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

WAVE LIFE SCIENCES LTD.

By: */s/ Keith C. Regnante*
Keith C. Regnante
Chief Financial Officer

Date: December 16, 2019

Wave Life Sciences Announces Discontinuation of Suvodirsen Development for Duchenne Muscular Dystrophy

No change from baseline in dystrophin observed in Phase 1 open-label extension study

Wave to host investor conference call at 8:00 a.m. ET today

CAMBRIDGE, Mass., December 16, 2019 – Wave Life Sciences Ltd. (Nasdaq: WVE), a clinical-stage genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases, today announced its decision to discontinue development of suvodirsen for patients with Duchenne muscular dystrophy (DMD) who have mutations amenable to exon 51 skipping, based on its interim analysis of the Phase 1 open-label extension (OLE) study. The results showed no change from baseline in dystrophin expression, as measured by western blot, with either the 3.5 mg/kg or 5 mg/kg doses of suvodirsen. No safety concerns or emerging safety signals were observed.

As a result of this decision, the company is immediately discontinuing the two suvodirsen trials, the OLE study and the Phase 2/3 DYSTANCE 51 trial. Patients will have a final follow-up visit, but no further doses will be administered, and patients will no longer undergo muscle biopsies. In addition, Wave is suspending further development of WVE-N531 for patients with mutations amenable to exon 53 skipping.

“We set out to restore meaningful levels of dystrophin in patients with Duchenne, and we failed to achieve this goal,” said Michael Panzara, MD, MPH, Chief Medical Officer of Wave Life Sciences. “These results are not what we expected, particularly given the promising data from our preclinical models, and we commit to further analyzing and understanding the results to aid in future research. I would like to extend our gratitude to the patients and families for their courage and participation in this program, as well as to our colleagues at Duchenne centers throughout the world whose advice and dedication made the execution of these studies possible. We will share additional findings from the suvodirsen development program so that the Duchenne community may benefit from its contributions to this study.”

The interim analysis was from a global multicenter OLE study of suvodirsen in patients who previously enrolled in a Phase 1 safety and tolerability study. A total of 36 patients enrolled in the OLE and received the target doses of either 3.5 mg/kg or 5 mg/kg. A biopsy of the deltoid muscle was performed prior to initial dosing in the OLE and, as of data cut-off for this interim analysis, follow-up deltoid muscle biopsies were available for 27 of 36 patients. Within the 5 mg/kg weekly infusion arm, 10 patients received follow-up muscle biopsies at 12 weeks and nine patients received follow-up biopsies at 22 weeks. Within the 3.5 mg/kg weekly infusion arm, eight patients received follow-up muscle biopsies at 22 weeks. Biopsies from both timepoints were analyzed as part of this interim analysis.

“The suvodirsen results are unexpected and deeply disappointing to us, and undoubtedly will be to the patients we aim to serve. We are grateful to be part of the Duchenne community and our organization has been shaped by their strength and resilience,” said Paul Bolno, MD, CEO of Wave Life Sciences. “While we did not achieve dystrophin restoration in this study, there is a rising tide in nucleic acid therapeutics, and we are fully committed to advancing genetic medicines in diseases of the central nervous system, eye and liver. We will work to rapidly incorporate our learnings, so that we can seek to deliver on the promise of our current and future pipeline. As previously announced, we look forward to reporting topline clinical data from our PRECISION-HD2 trial in Huntington’s disease by the end of 2019.”

Revised Cash Guidance

As a result of the decisions announced above, Wave now expects that its existing cash and cash equivalents, together with expected and committed cash from existing collaborations, will enable Wave to fund its operating and capital expenditure requirements into the third quarter of 2021.

Investor Conference Call and Webcast

Wave management will host an investor conference call today at 8:00 a.m. ET. The conference call may be accessed by dialing +1 (866) 220-8068 for participants based in the United States or +1 (470) 495-9153 for participants based outside the United States, and entering conference ID 9967079. The live webcast may be accessed by visiting the "For Investors & Media" section of the Wave Life Sciences website at www.ir.wavelifesciences.com. Following the webcast, a replay will be available on the website.

About Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a fatal X-linked genetic neuromuscular disorder caused predominantly by out-of-frame deletions in the dystrophin gene, resulting in absent or defective dystrophin protein. Dystrophin protein is needed for normal muscle maintenance and operation. Because of the genetic mutations in DMD, the body cannot produce functional dystrophin, which results in progressive and irreversible loss of muscle function, including the heart and lungs. Worldwide, DMD affects approximately one in 5,000 newborn boys.

About Suvodirsen

Suvodirsen is an investigational stereopure oligonucleotide previously in development as a treatment for patients with Duchenne muscular dystrophy (DMD) who have genetic mutations amenable to exon 51 skipping. Wave initiated clinical development of suvodirsen in November 2017 and completed a Phase 1 safety and tolerability study in early 2019. Based on an interim analysis from a Phase 1 Open Label Extension (OLE) study conducted in December 2019, Wave discontinued development of suvodirsen.

Approximately 13% of DMD patients have mutations amenable to treatment with an exon 51 skipping therapy. Exon-skipping technology is intended to induce cellular machinery to 'skip over' a targeted exon and restore the reading frame, resulting in the production of internally truncated, but functional dystrophin protein.

About Wave Life Sciences

Wave Life Sciences (Nasdaq: WVE) is a clinical-stage genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases. Wave aspires to develop best-in-class medicines across multiple therapeutic modalities using PRISM™, the company's proprietary discovery and drug development platform that enables the precise design, optimization and production of stereopure oligonucleotides. Driven by a resolute sense of urgency, the Wave team is targeting a broad range of genetically defined diseases so that patients and families may realize a brighter future. To find out more, please visit www.wavelifesciences.com and follow Wave on Twitter @WaveLifeSci.

Forward-Looking Statements

This press release contains forward-looking statements concerning our goals, beliefs, expectations, strategies, objectives and plans, and other statements that are not necessarily based on historical facts, including statements regarding the following, among others: our commitment to advancing genetic medicines in diseases of the central nervous system, eye and liver; our intent to rapidly incorporate our learnings from the Phase 1 OLE study; our ability to deliver on the promise of our current and future pipeline; our plans to report topline clinical data from the PRECISION-HD2 trial; the future performance and results of our programs in clinical trials and in preclinical development; the potential benefits of PRISM and our stereopure oligonucleotides compared with stereorandom oligonucleotides; the benefit of nucleic acid therapeutics generally; and the anticipated duration of our cash runway. Actual results may differ materially from those indicated by these forward-looking statements as a result of various important factors, including the following: our ability to finance our drug discovery and development efforts and to raise additional capital when needed; the ability of our preclinical programs to produce data sufficient to support our clinical trial applications and the timing thereof; our ability to continue to build and maintain the company infrastructure and personnel needed to achieve our goals; the

clinical results of our programs, which may not support further development of product candidates; actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials; our effectiveness in managing future clinical trials and regulatory processes; the effectiveness of PRISM; the continued development and acceptance of oligonucleotides as a class of medicines; our ability to demonstrate the therapeutic benefits of our candidates in clinical trials, including our ability to develop candidates across multiple therapeutic modalities; our dependence on third parties, including contract research organizations, contract manufacturing organizations, collaborators and partners; our ability to manufacture or contract with third parties to manufacture drug material to support our programs and growth; our ability to obtain, maintain and protect intellectual property; our ability to enforce our patents against infringers and defend our patent portfolio against challenges from third parties; and competition from others developing therapies for similar uses, as well as the information under the caption "Risk Factors" contained in our most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) and in other filings we make with the SEC from time to time. We undertake no obligation to update the information contained in this press release to reflect subsequently occurring events or circumstances.

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Exhibit 99.2

Wave Life Sciences

Corporate Presentation

December 16, 2019

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.

Pipeline spanning multiple modalities, novel targets

THERAPEUTIC AREA/MODALITY	TARGET	DISCOVERY	CANDIDATE	CLINICAL	ESTIMATED U.S. PREVALENCE*	PARTNER
CNS						
Huntington's disease Allele – selective silencing	**WVE-120101** mHTT SNP1			Phase 1b/2a	~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 Allele – selective silencing	C9orf72				~1,800 (ALS) ~7,000 (FTD)	Takeda 50:50 option
Spinocerebellar ataxia 3 Silencing	ATXN3				~4,500	Takeda 50:50 option
CNS diseases	Multiple†					Takeda milestones & royalties
OPHTHALMOLOGY						
Retinal diseases	USH2A and multiple					100% global
HEPATIC						
Metabolic liver diseases Silencing	Multiple					Pfizer milestones & royalties
OTHER						
ADAR RNA-editing	Multiple					100% global

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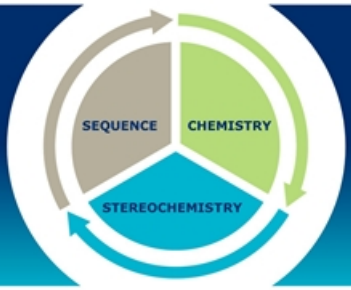
*Estimates of U.S. prevalence and addressable population by target based on publicly available data and are approximate; for Huntington's disease, numbers approximate manifest and pre-manifest populations, respectively.
†During a four-year term, Wave and Takeda may collaborate on up to six preclinical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

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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Designing the optimal, stereopure medicine

STANDARD OLIGONUCLEOTIDE APPROACHES

Pharmacologic properties include >500,000 permutations in every dose

↓

Impact:
Unreliable therapeutic effects
Unintended off-target effects

WAVE RATIONAL DESIGN

Control of stereochemistry enables the design and manufacture of oligonucleotides with one defined and consistent profile

↓

Impact:
Potential for best-in-class medicines that can address difficult-to-treat diseases

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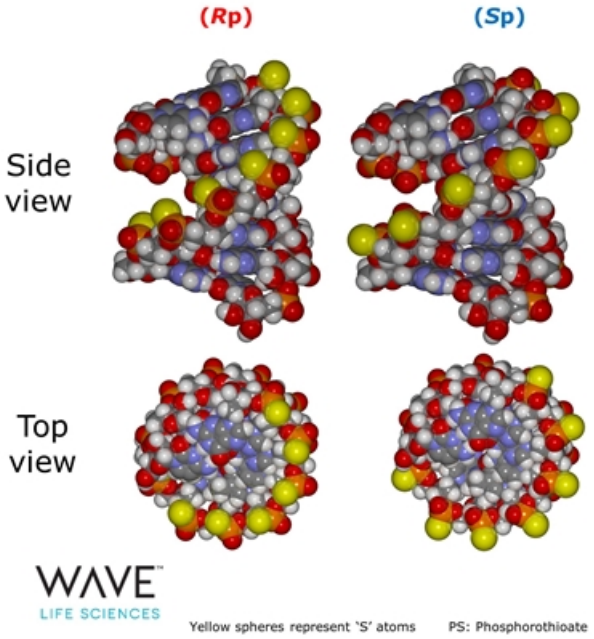
Stereochemical diversity

- Exponential diversity arises from uncontrolled stereochemistry



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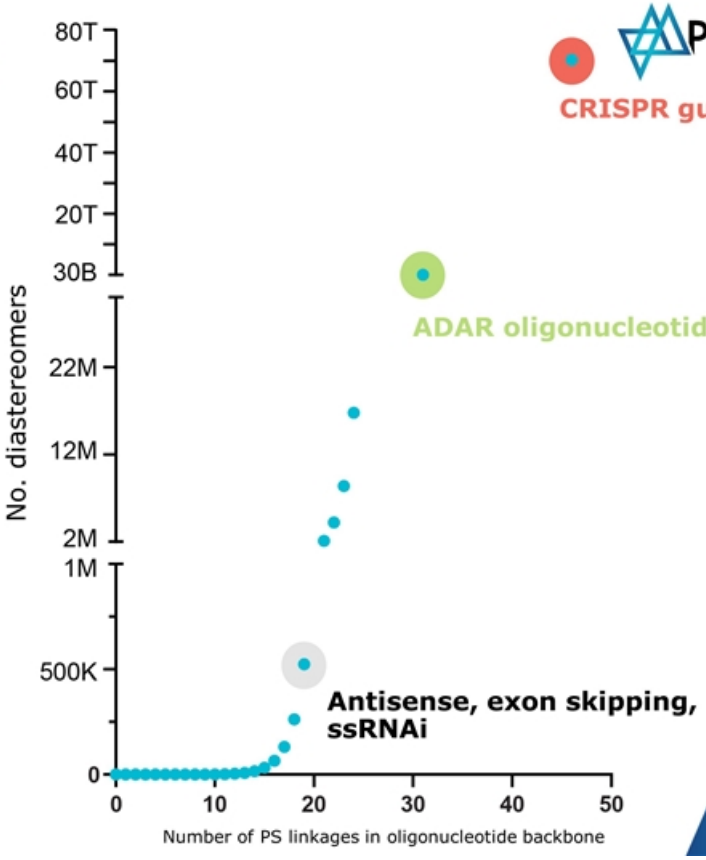
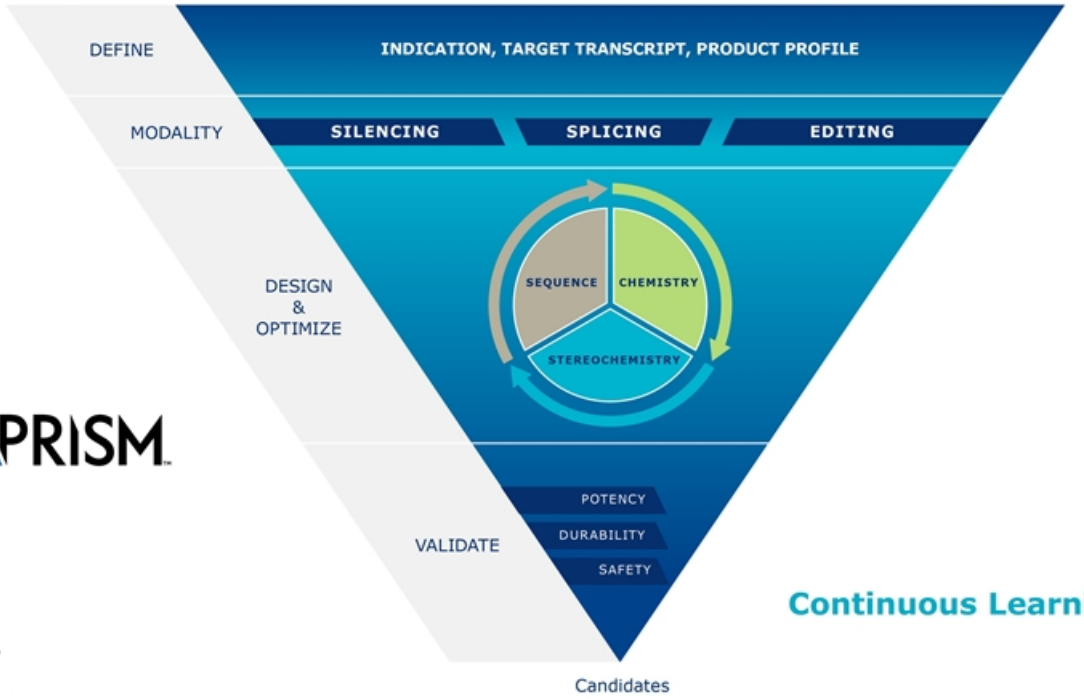
Yellow spheres represent 'S' atoms PS: Phosphorothioate



PRISM CRISPR guide

PRISM platform enables rational drug design



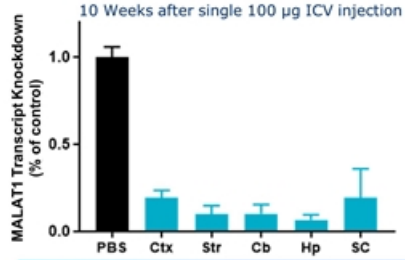
Continuous Learning

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

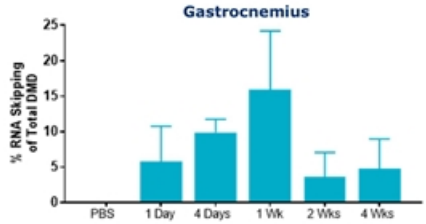
CNS

MALAT1 Transcript Knockdown in Mice
10 Weeks after single 100 µg ICV injection



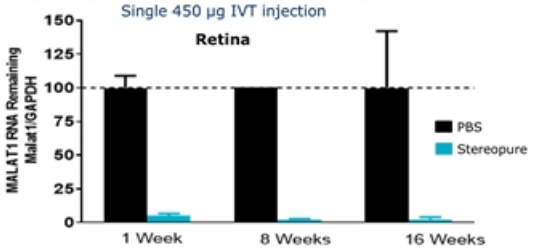
Muscle

DMD: Percent Skipped Transcript in *mdx*23 Mice
Single 150 mg/kg IV injection



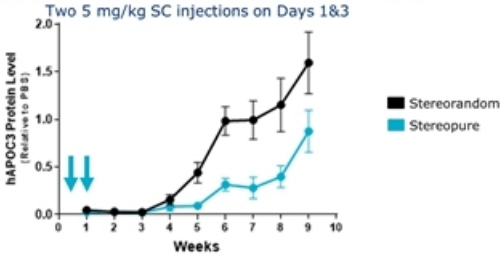
Eye

MALAT1 Knockdown in Non-Human Primates
Single 450 µg IVT injection



Liver

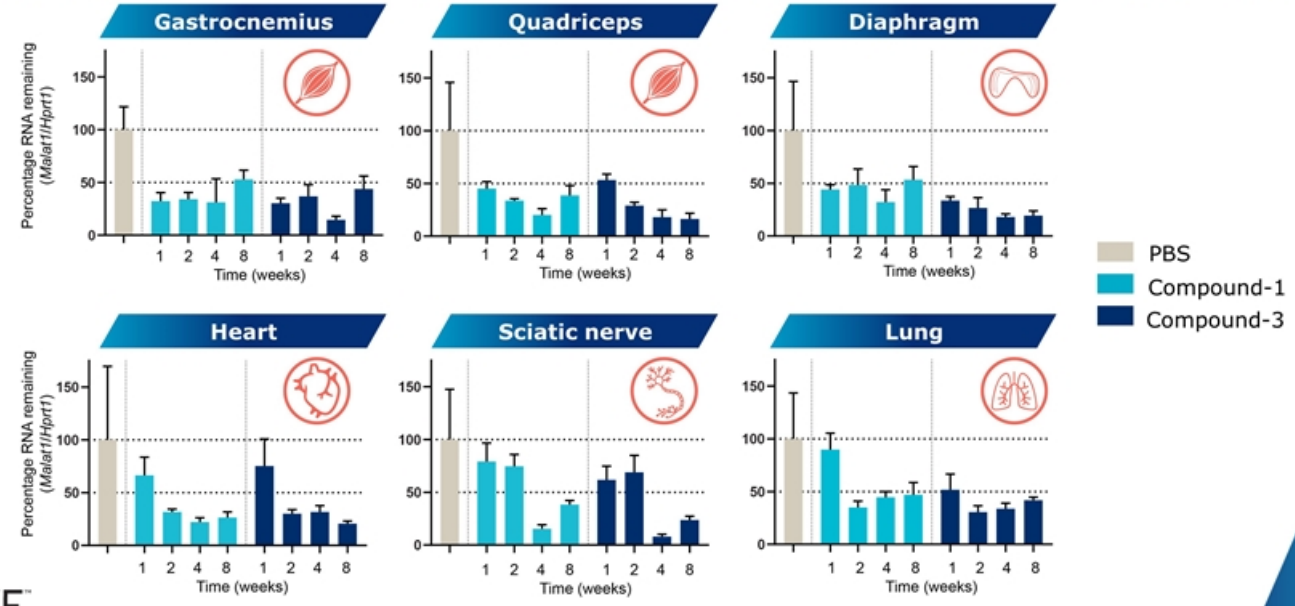
Knockdown of Serum hAPOC3 Protein Levels in Mice
Two 5 mg/kg SC injections on Days 1&3



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

Broad tissue distribution and durable target engagement

Single IV injection of Wave compounds targeting *MALAT1* (human equivalent of 1.6 mg/kg)

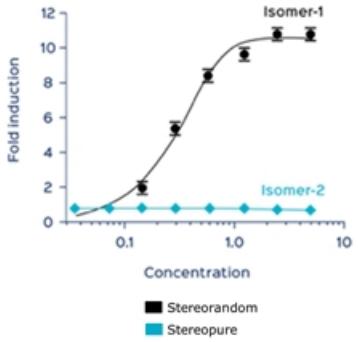


Mice were dosed with a single IV injection (25 mg/kg) of *MALAT1*-targeting compound, and tissues were assessed for RNA expression 1-, 2-. 4-, and 8-weeks post-dose. Relative percentage of *MALAT1* RNA to PBS-treated mice (n=5 per group). *MALAT1* RNA levels are normalized to Hprt1.

Stereochemistry affects immune activation

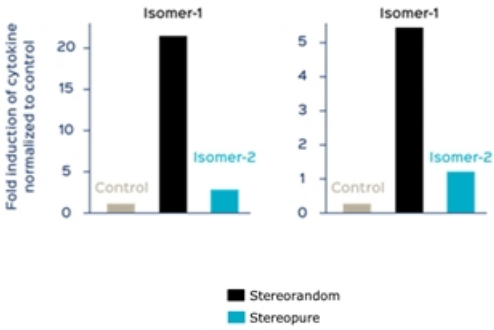
Human TLR9 Activation

Human TLR9 activation assay with 5mC modified CpG containing MOE gapmer



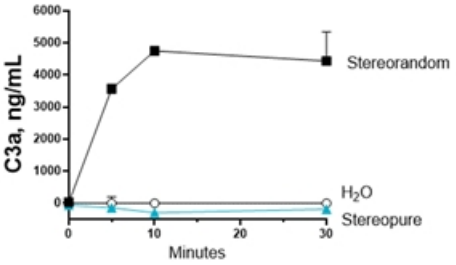
Cytokine Induction

Cytokine induction in human PBMC assay



Complement Activation

Complement activation in non-human primate serum assay



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Data represented in this slide from *in vitro* studies. MOE = 2′-O-methoxyethylribose; PBMC = peripheral blood mononuclear cell; TLR9 = toll-like receptor 9.

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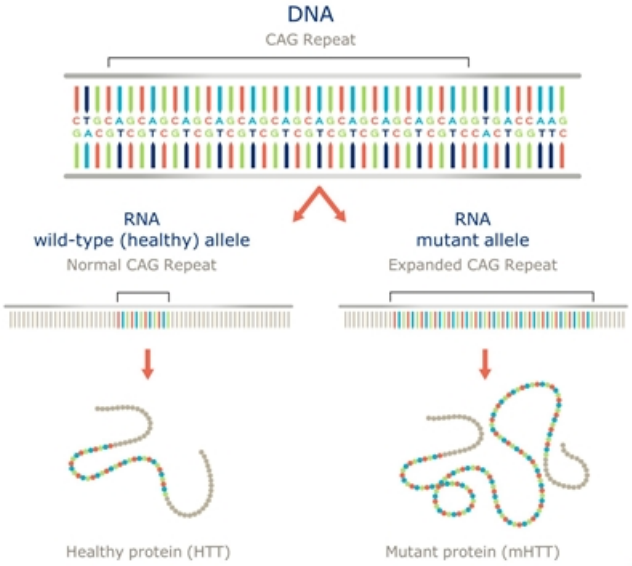
WVE-120101
WVE-120102
Huntington's Disease

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; suppression may have detrimental long-term consequences
- 30,000 people with Huntington's disease in the US; another 200,000 at risk of developing the condition



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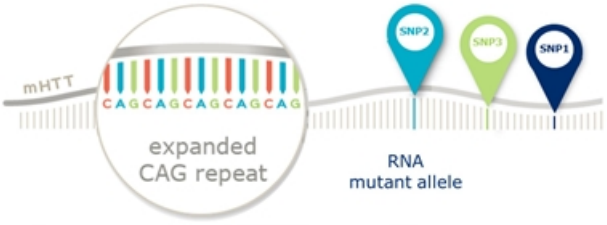
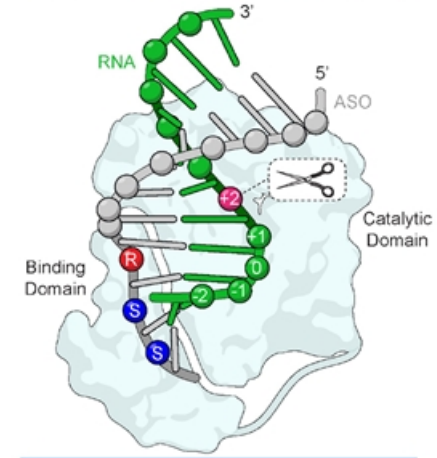
Sources: Auerbach W, et al. *Hum Mol Genet.* 2001;10:2515-2523. Dragatsis I, et al. *Nat Genet.* 2000;26:300-306. Leavitt BR, et al. *J Neurochem.* 2006;96:1121-1129. Nasir J, et al. *Cell.* 1995;81:811-823. Reiner A, et al. *J Neurosci.* 2001;21:7608-7619. White JK, et al. *Nat Genet.* 1997;17:404-410. Zeitlin S, et al. *Nat Genet.* 1995;11:155-163. Carroll JB, et al. *Mol Ther.* 2011;19:2178-2185. Huntington Disease Society of America (HDSA). What is Huntington's disease? Available at: https://hdsa.org/what-is-hd/overview-of-huntingtons-disease/ Accessed: November 2, 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.

Two simultaneous Phase 1b/2a clinical trials

- PRECISION-HD is a global clinical program consisting of the PRECISION-HD1 trial evaluating WVE-120101 targeting SNP1 and the PRECISION-HD2 trial evaluating WVE-120102 targeting SNP2
  - Two parallel, multicenter, double-blind, randomized, placebo-controlled Phase 1b/2a clinical trials for WVE-120101 and WVE-120102, administered intrathecally, with single-ascending dose and multiple-ascending dose portions
  - Primary objective: Assess safety and tolerability of intrathecal doses in early manifest HD patients
  - Key additional objectives: Measurement of total HTT and mHTT; exploratory pharmacokinetic (PK), pharmacodynamic (PD), clinical and MRI endpoints
  - Key inclusion criteria: age ≥25 to ≤65, stage I or II HD who have screened positively for the presence of SNP1 or SNP2
  - Expected to enroll approximately 50 patients per trial
  - **Topline data expected to include: summary of clinical safety results, degree of mHTT protein lowering in CSF at 20 weeks, the ratio of total HTT versus mHTT in CSF at 20 weeks**
- Open-label extension (OLE) study initiated for PRECISION-HD2 outside of the U.S. to allow for continued dosing and clinical assessments
  - PRECISION-HD1 OLE expected to initiate in 2020
- Intend to explore efficacy in early manifest and pre-manifest HD patient populations

Topline data readout for PRECISION-HD2 expected by YE 2019

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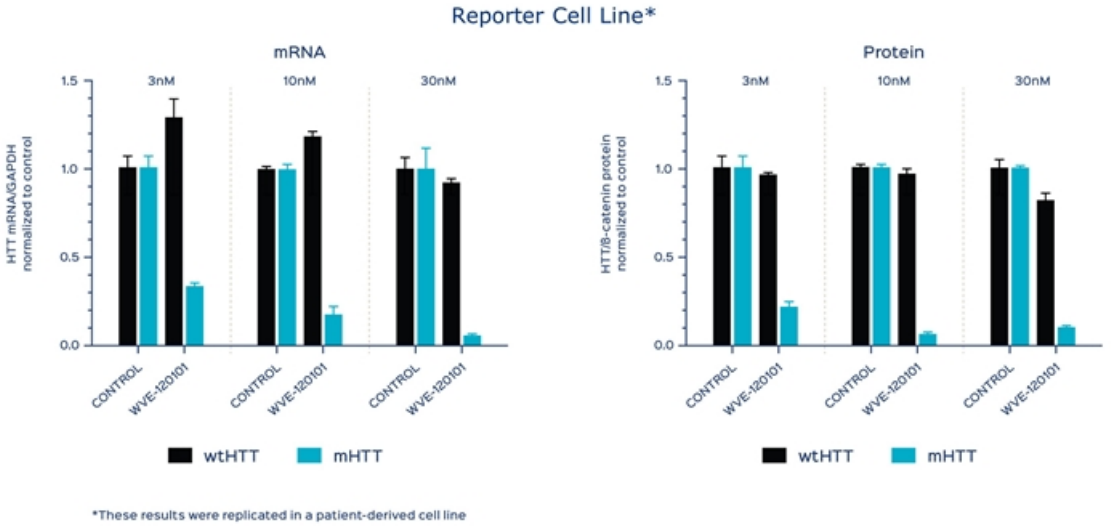
Selective reduction of mHTT mRNA & protein

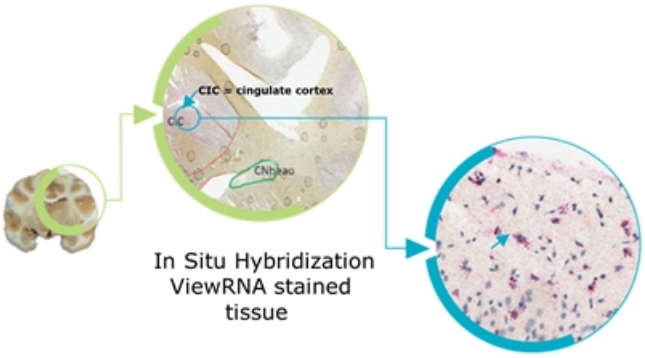


*These results were replicated in a patient-derived cell line

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

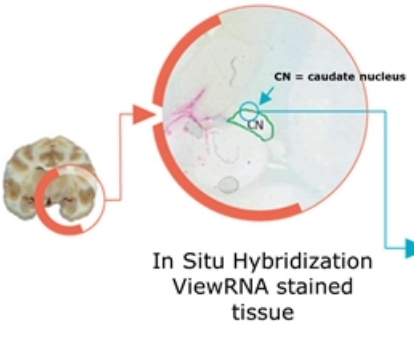
- WVE-120101 and WVE-120102 distribution in cynomolgus non-human primate brain following intrathecal bolus injection



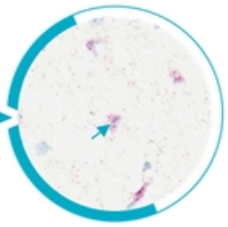
In Situ Hybridization ViewRNA stained tissue

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

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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.

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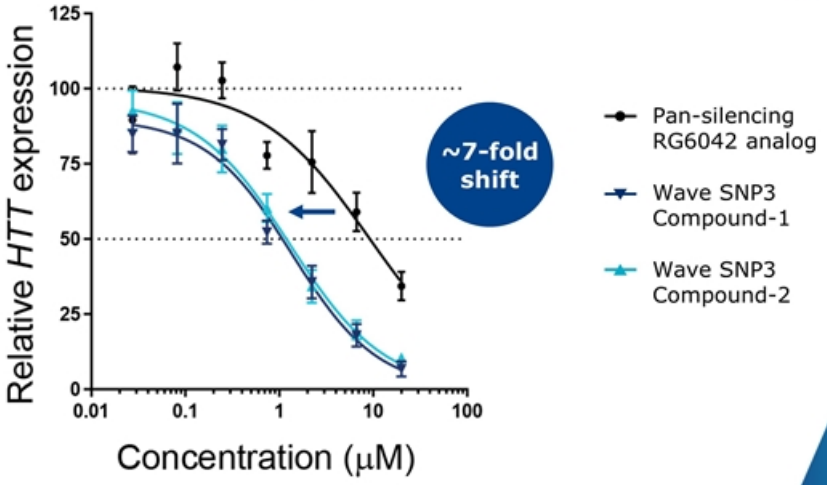
SNP3 Preclinical Program
Huntington's Disease

Potent mutant HTT knockdown activity

Wave allele-selective compounds are more potent than pan-silencing RG6042 analog in preclinical study involving patient-derived neurons

- Greater knockdown of mutant HTT as compared to pan-silencing compound

Homozygous iCell Neurons



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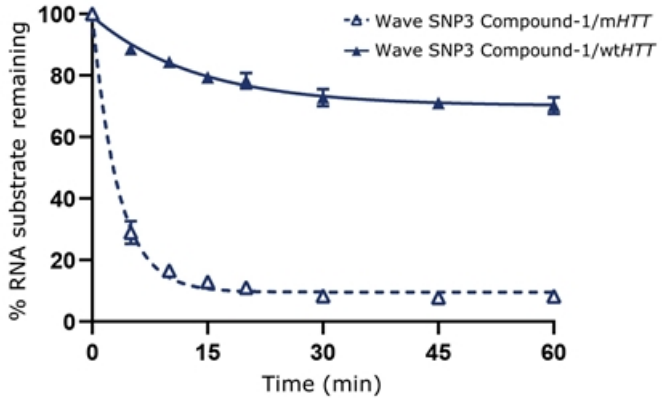
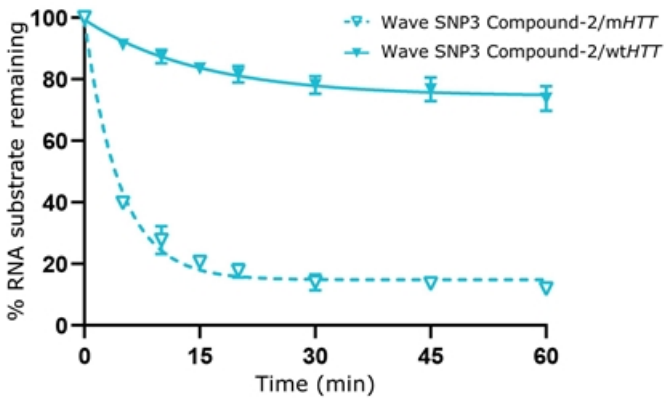
HTT mRNA remaining in iCell neurons (homozygous for SNP) incubated with the indicated ASO under free-uptake conditions. Data show mean ± sem (n=4).

Stereopure oligonucleotides are selective *in vitro*

Stereopure isomers targeting a SNP variant promote RNase H-mediated degradation of mutant *HTT* while sparing wild-type *HTT*

Biochemical RNase H assays





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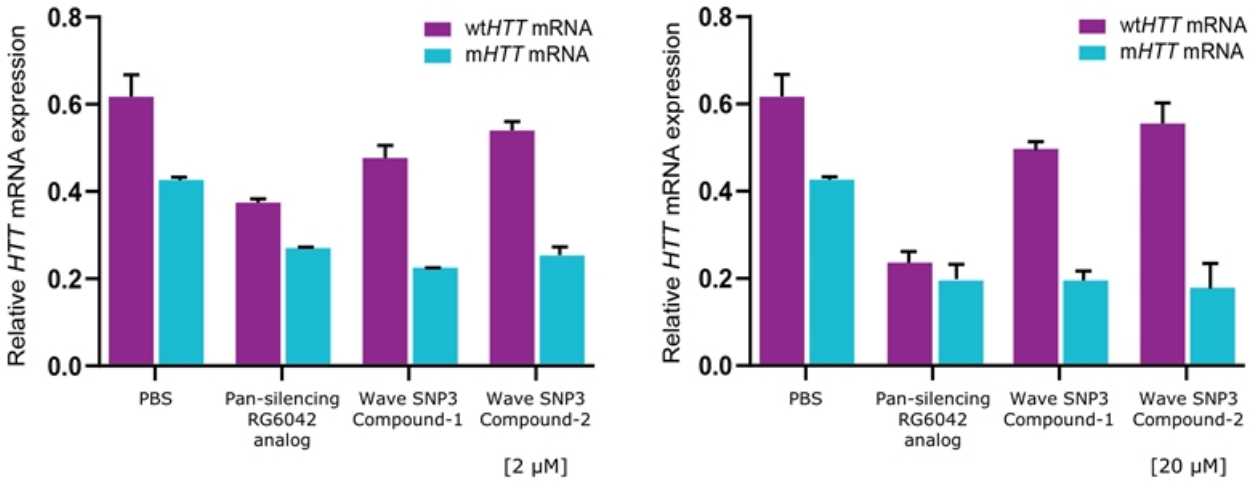
RNase H experiments performed with synthetic RNA substrates corresponding to m*HTT* and wt*HTT* variants (S:E = 100:1; n=2). Percentage of the indicated full-length RNA substrate remaining over time is plotted for the stereopure SNP3 Compound-1 (left) and stereopure SNP3 Compound-2 (right). Abbreviations: S, substrate; E, enzyme.

Demonstration of allele-selective silencing

Stereopure compounds selectively deplete mutant *HTT* mRNA

No loss of selectivity with increasing concentrations



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Neurons were derived from GM21756 patient-derived fibroblasts (heterozygous for SNP) and treated with 2.2 µM (left) or 20 µM (right) of the indicated ASO under gymnotic conditions for 7 days. RNA was quantified and normalized to *TUBB3*. Data are mean ± sem (n=3). Percentage of remaining wt*HTT* and m*HTT* mRNA is indicated.

In vivo model to assess target engagement and durability

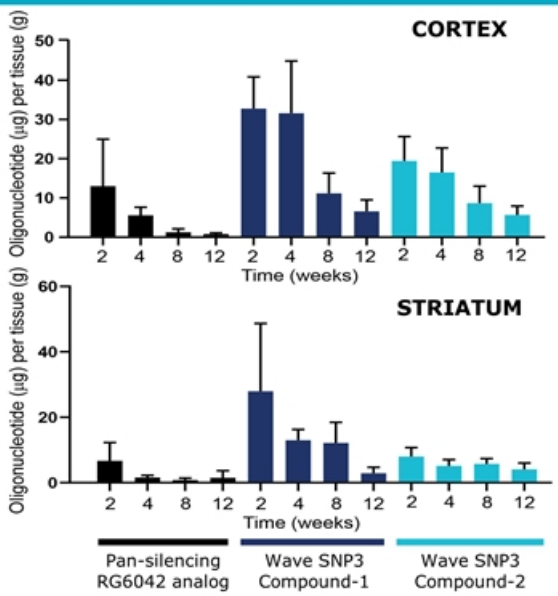
BACHD mouse model

- Expressed transcript includes SNP3 variant that Wave compounds are targeting
- Model is homozygous for mutant *HTT* with SNP3 (only has one type of *HTT*)
- Over-expresses m*HTT* (multiple gene copies)
- No ability to assess allele selectivity

Oligonucleotide concentration in tissues

- Achieved good tissue exposure over 12-weeks in BACHD cortex and striatum

Tissue exposure over time



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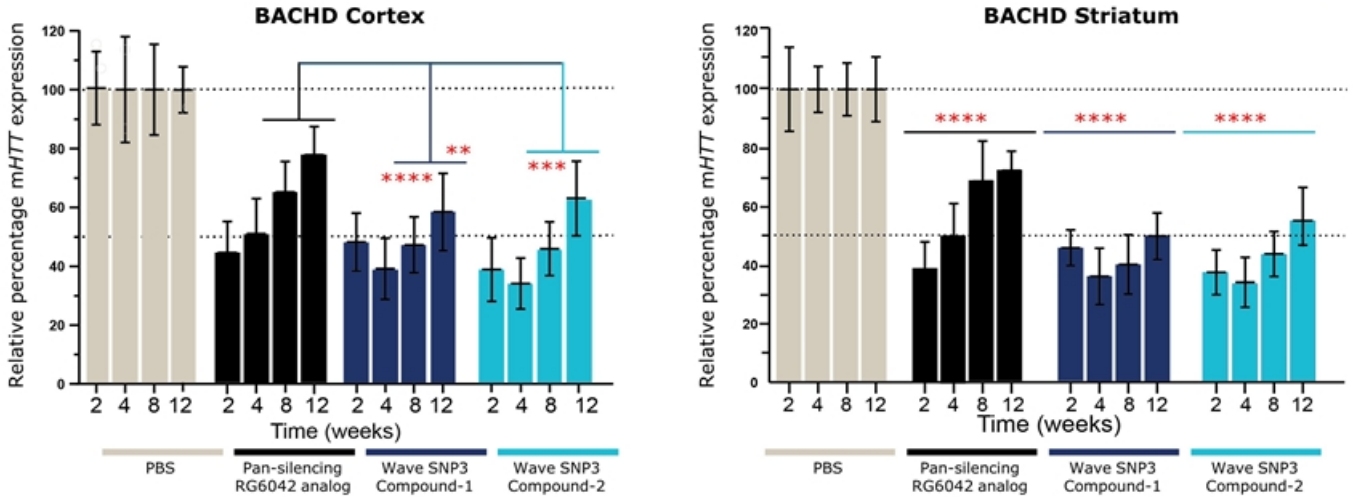
Oligonucleotide or PBS (3 x 100 µg ICV) was delivered to BACHD mice. Oligonucleotides were quantified by ELISA.

Durable *in vivo* mutant *HTT* knockdown with stereopure SNP3 compounds

Knockdown persists for 12 weeks



BACHD model only has mutant HTT (no wild-type HTT)

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Oligonucleotide or PBS (3 x 100 mg ICV) was delivered to BACHD mice. Relative percentage of HTT/TUBB3 mRNA in cortex with respect to levels in PBS-treated mice is shown at 2-12 weeks post-injection. Statistics: All oligo treatment groups are statistically significantly different from PBS; One-way ANOVA ****, P≤0.0001. Wave SNP3 Compound-1 and Compound-2 are also significantly different from RG6042 analog at 8 and 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 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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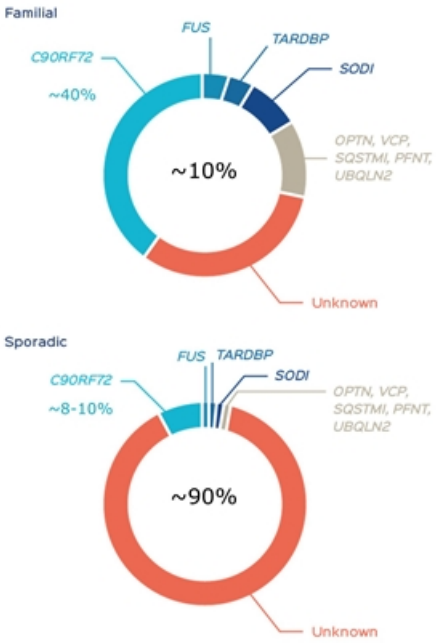
Source: DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. *Neuron.* 2011;72:245-256. Renton AE, Majounie E, Waite A, et al. *Neuron.* 2011;72:257-268.

Amyotrophic lateral sclerosis

- Fatal neurodegenerative disease characterized by the progressive degeneration of motor neurons in the brain and spinal cord
- Affects approximately 15,000-20,000 people in the US with a median survival of three years
- C9orf72 is present in approximately 40% of familial ALS and 8-10% of sporadic ALS; currently the most common demonstrated mutation related to ALS, far more so than SOD1 or TDP-43
- Pathogenic transcripts of the C9orf72 gene contain hundreds to thousands of hexanucleotide repeats compared to 2-23 in wild-type transcripts; dominant trait with high penetrance



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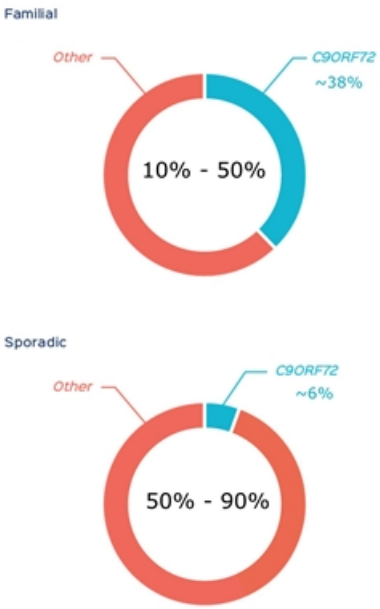
Source: Renton AE, Chiò A, Traynor BJ. State of play in amyotrophic lateral sclerosis genetics. *Nat Neurosci*. 2014;17:17–23.

Frontotemporal dementia

- Progressive neuronal atrophy with loss in the frontal and temporal cortices characterized by personality and behavioral changes, as well as gradual impairment of language skills
- Affects approximately 55,000 people in the US
- Second most common form of early-onset dementia after Alzheimer's disease in people under the age of 65
- Up to 50% of FTD patients have a family history of dementia, many inheriting FTD as an autosomal dominant trait with high penetrance
- Pathogenic transcripts of the C9orf72 gene contain hundreds to thousands of hexanucleotide repeats compared to 2-23 in wild-type transcripts



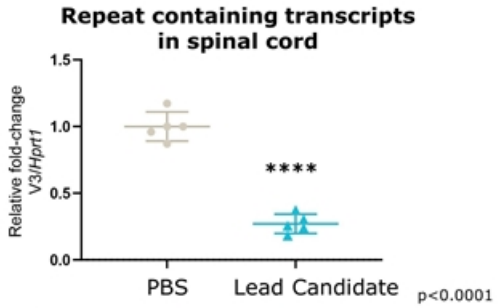
Sources: Stevens M, et al. Familial aggregation in frontotemporal dementia. *Neurology*. 1998;50:1541-1545. Majounie E, et al. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. *Lancet Neurol.* 2012;11:323-330.

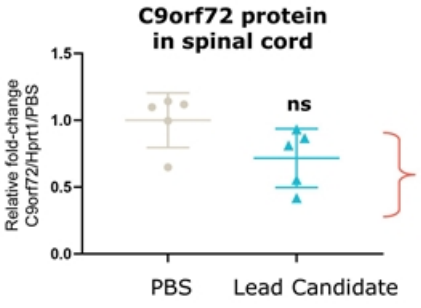
C9orf72 program: Allele-selective silencing *in vivo*

- 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
- **Wave's approach:** Selectively silence the GGGGCC repeat containing transcript while minimizing the impact on normal C9orf72 protein

Selective silencing of C9orf72 *in vivo* (transgenic mouse)

Reduction of repeat containing transcripts





Protein preservation

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.

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Ophthalmology

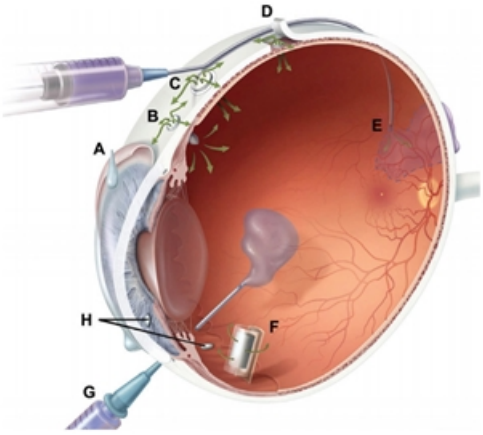
Stereopure oligonucleotides for inherited retinal diseases (IRDs)

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



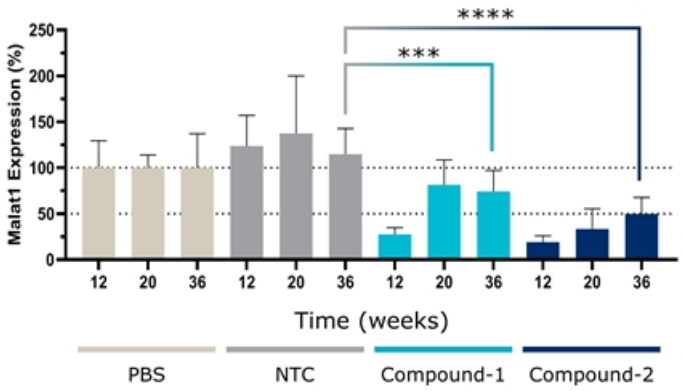
Intravitreal injection

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

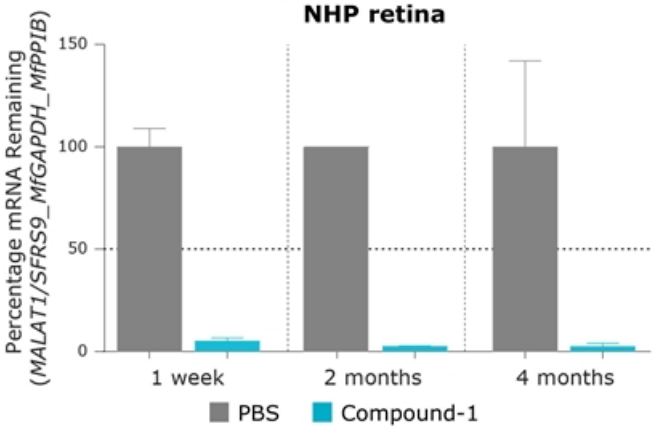
~50% *MALAT1* knockdown at 9 months

***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**



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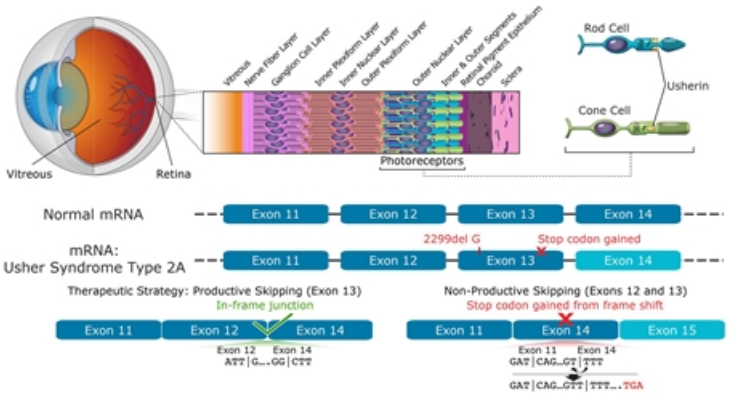
Mouse: Compound or PBS (1 x 50 mg IVT) was delivered to C57BL6 mice. Relative percentage of Malat1 RNA in the posterior of the eye (retina, choroid, sclera) to PBS-treated mice is shown at 12, 20 and 36 weeks post-single injection. Statistics: Compound-2 Malat1 levels are significantly different from 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.

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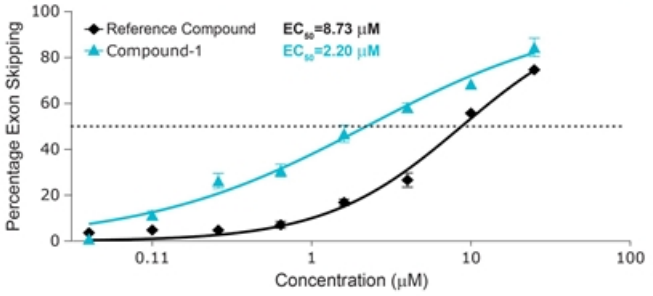
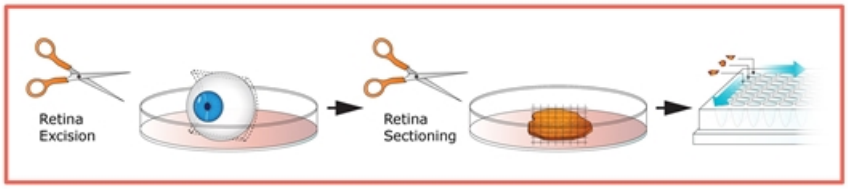
Sources: Boughman et al., 1983. *J Chron Dis.* 36:595-603; Seyedahmadi et al., 2004. *Exp Eye Res.* 79:167-173; Liu et al., 2007. *Proc Natl Acad Sci USA* 104:4413-4418.

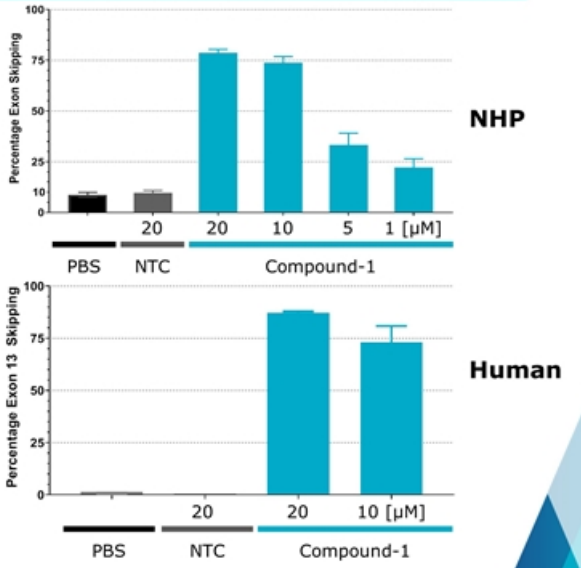
Potent USH2A exon 13 skipping with stereopure compound in *vitro* and *ex vivo*

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





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



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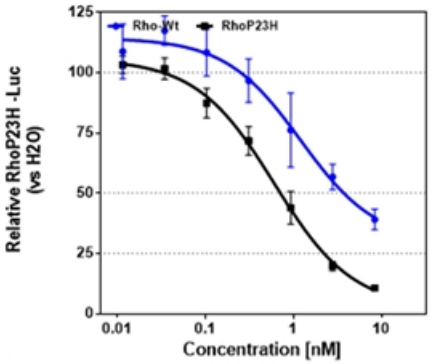
Left: Compounds were added to Y79 cells under free-uptake conditions. Exon skipping was evaluated by Taqman assays. *USH2A* transcripts were normalized to *SRSF9*. Data are mean±s.d., n=2. Reference Compound: van Diepen *et al.* 2018. Antisense oligonucleotides for the treatment of eye disease. W02018055134A1. 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.

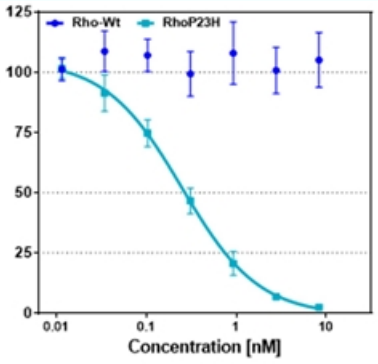
Allele-selective reduction of SNP-containing allele for adRP associated with Rhodopsin P23H mutation

- **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.

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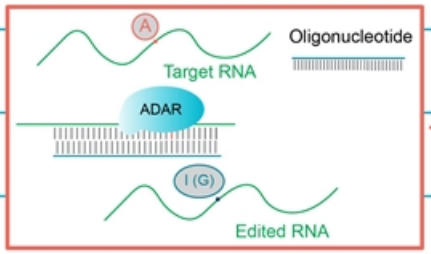
ADAR-mediated RNA editing

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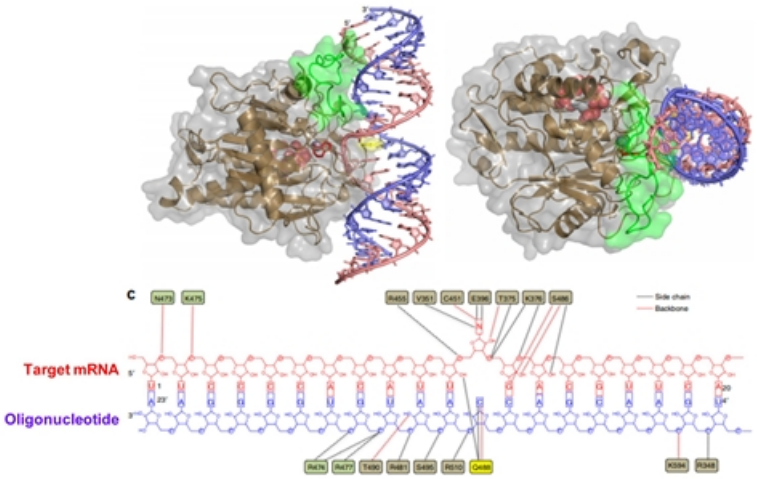
I (G): ADAR converts A>I, I is recognized as G by all cellular machinery; ADAR: Adenosine Deaminase Acting on RNA; ORF: Open reading frame

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

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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

Wave's ADAR approach has several potential advantages over existing technologies

PRISM

Existing RNA editing technologies		Wave's RNA editing platform
Use unmodified RNA	Stability	Fully chemically-modified stereopure oligonucleotides
Require AAV or lipid nano particle delivery	Delivery	Free uptake into tissues
Require exogenous protein (e.g. CAS13 or chimeric ADAR)	Editing	Uses endogenous ADAR for editing

Single oligonucleotide through free uptake is sufficient for editing

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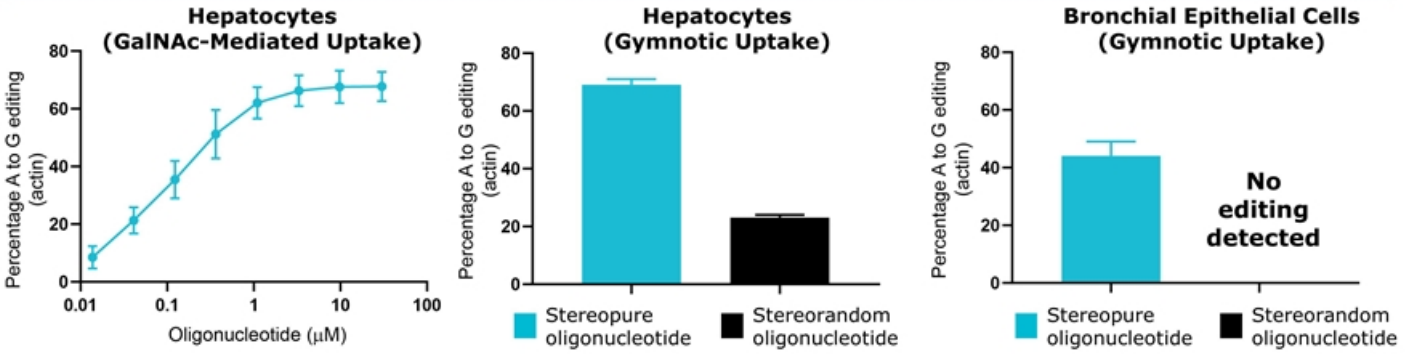
RNA-editing with endogenous ADAR achieved across multiple primary human cell types

Editing UAG Site in Actin mRNA in Primary Human Cell Lines



- Stereochemistry significantly increases editing across all cell lines tested, especially for gymnotic delivery
- GalNAc-conjugated fully-modified stereopure oligonucleotide can be used for targeted editing in hepatocytes; *in vitro* experiments suggest an EC50 of ~100 nM in primary hepatocytes
- *In vivo* editing with fully-modified stereopure oligonucleotide studies underway

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***In vivo* editing data expected in 2020**

Anticipated upcoming Wave milestones

CNS

- **By YE 2019:** Topline data readout from PRECISION-HD2 Phase 1b/2a trial in Huntington's disease
- **Early 2020:** Topline data readout from PRECISION-HD1 Phase 1b/2a trial in Huntington's disease
- **2H 2020:** Initiation of clinical development of C9orf72 program in ALS and FTD

Ophthalmology

- **2020:** Advance USH2A exon-skipping program

RNA-editing

- **2020:** *In vivo* ADAR editing data

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Realizing the potential of genetic medicines

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