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): May 11, 2020

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

Singapore	**001-37627**	**00-0000000**
(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 (see General Instruction A.2. below):

☐ 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 2.02 Results of Operations and Financial Condition.

On May 11, 2020, Wave Life Sciences Ltd. (the "Company") announced its financial results for the quarter ended March 31, 2020. The full text of the press release issued in connection with the announcement is furnished as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated by reference herein.

Item 7.01 Regulation FD Disclosure.

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. On May 11, 2020, 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.

The information in these Items 2.02 and 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 9.01 Financial Statements and Exhibits.

(d) Exhibits

The following exhibits relating to Items 2.02 and 7.01 are furnished and not filed:

Exhibit No.	Description
99.1	Press Release issued by Wave Life Sciences Ltd. dated May 11, 2020
99.2	Corporate Presentation of Wave Life Sciences Ltd. dated May 11, 2020
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/ Paul B. Bolno, M.D.*
Paul B. Bolno, M.D.
President and Chief Executive Officer

Date: May 11, 2020

Wave Life Sciences Reports First Quarter 2020 Financial Results and Provides Business Update

Data from both PRECISION-HD clinical trials expected in 2H 2020

Advancing clinical neurology pipeline – SNP3 and C9orf72 programs on track to initiate clinical development in 2H 2020

First ADAR-mediated RNA-editing data in non-human primates demonstrates editing efficiencies of up to 50%

Wave to host investor conference call and webcast at 8:30 a.m. ET today

CAMBRIDGE, Mass., May 11, 2020 – 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 financial results for the first quarter ended March 31, 2020 and provided a business update.

"During the last few months, our team has done a tremendous job of navigating the realities of the global COVID-19 pandemic, while making substantial progress on our critical priorities, including delivering on a key 2020 milestone, our initial *in vivo* RNA-editing dataset. We are working tirelessly to keep our clinical trials ongoing, our preclinical programs moving towards clinical development, and our discovery work on track, all while supporting each other and our communities during this difficult time," said Paul Bolno, MD, MBA, President and Chief Executive Officer of Wave Life Sciences.

"Our PRECISION-HD clinical trials of WVE-120101 and WVE-120102, two investigational compounds designed to selectively target mutant HTT for the treatment of Huntington's disease, are ongoing. While the pandemic has impacted several global clinical trial sites, the commitment of our patients and investigators remains resolute, speaking to the high unmet need for disease modifying therapeutics for this devastating disease. In addition, we currently remain on track to initiate clinical development for two additional neurological programs in the second half of 2020. Lastly, today we are announcing new data from our ADAR-mediated RNA-editing program and I look forward to sharing further updates on this emerging platform capability later this year."

Recent business highlights

PRECISION-HD programs for Huntington's disease (HD): Wave is developing a unique portfolio of investigational stereopure oligonucleotides designed to selectively target the mutant allele of the huntingtin (mHTT) gene, while leaving the wild-type (wtHTT) relatively intact.

PRECISION-HD2:

- The PRECISION-HD2 Phase 1b/2a clinical trial, Wave's clinical trial investigating WVE-120102, a stereopure oligonucleotide designed to selectively target the mHTT mRNA transcript that contains the SNP rs362331 (SNP2) for HD, is ongoing.
- Data from the 32 milligram (mg) dose cohort of the PRECISION-HD2 trial are currently expected in the second half of 2020.

- An open-label extension (OLE) study open to patients outside of the U.S. who participated in the Phase 1b/2a PRECISION-HD2 trial is ongoing.

PRECISION-HD1:

- In March 2020, Wave initiated a 32 mg dose cohort in the ongoing PRECISION-HD1 Phase 1b/2a clinical trial of WVE-120101, a stereopure oligonucleotide designed to selectively target the mHTT mRNA transcript that contains the SNP rs362307 (SNP1) for HD.
- Wave currently expects to deliver topline clinical data from the PRECISION-HD1 trial, including the 32 mg dose cohort, in the second half of 2020.
- An open-label extension (OLE) study open to patients outside of the U.S. who participated in the Phase 1b/2a PRECISION-HD1 trial is ongoing.

PRECISION-HD trials:

- Wave continues to work closely with the PRECISION-HD clinical trial sites to monitor the impact of the evolving COVID-19 pandemic. If global restrictions continue or worsen, the ability to evaluate patients in both of the PRECISION-HD trials as planned may be impacted.
- Wave is assessing the potential for a next higher dose cohort to be added to both PRECISION-HD trials.

SNP3 program for HD: Wave is advancing a third HD program, which is designed to selectively target an undisclosed SNP on the mHTT mRNA transcript (SNP3), while leaving the wild-type (wtHTT) relatively intact.

- Wave expects to initiate clinical development of its SNP3 program in the second half of 2020.

C9orf72 program for ALS and FTD: Wave's C9orf72 program is designed to selectively target the transcripts containing the hexanucleotide repeat expansion (G4C2) in the *C9orf72* gene.

- Wave is advancing its C9orf72 preclinical program to potentially treat amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) and expects to initiate clinical development in the second half of 2020.

Central nervous system (CNS) programs in collaboration with Takeda: Wave is leveraging its learnings from PRISM™ to design additional stereopure oligonucleotides with optimized profiles for CNS indications, including Parkinson's, Alzheimer's and others, as part of its ongoing collaboration with Takeda.

- In the first quarter, Wave achieved target validation *in vivo* with a lead compound for a second program and expects to achieve target validation for a third program in 2020.

RNA editing: Wave is designing a novel RNA-editing platform capability using endogenous ADAR (adenosine deaminases acting on RNA) enzymes via free uptake (non-viral, non-LNP) of RNA-editing oligonucleotides, which has the potential to be a best-in-class RNA-editing modality.

- Today, Wave announced it has achieved successful RNA editing of ACTB (Beta-actin) mRNA in non-human primates (NHPs) via endogenous ADARs using stereopure GalNAc-conjugated oligonucleotides. In an ongoing proof-of-concept study, Wave oligonucleotides demonstrated up to 50% A to I (G) editing of ACTB mRNA in the liver of NHPs two-days post-last dose. To the company's knowledge, these are the first publicly available data that demonstrate successful RNA editing *in vivo* in NHPs.
- This RNA-editing platform is expected to be applicable for a wide range of disease targets. Wave has previously shown that its RNA-editing oligonucleotides achieved editing across multiple distinct transcripts in primary human hepatocytes and this *in vitro* data will also be presented at the upcoming American Society of Gene & Cell Therapy (ASGCT) Annual Meeting, being held virtually May 12 – May 15.
- Wave expects to share additional *in vivo* ADAR-mediated RNA-editing data and to announce its first RNA-editing program in 2020.

First Quarter 2020 Financial Results and Financial Guidance

Wave reported a net loss of $47.5 million in the first quarter of 2020 as compared to $44.2 million in the same period in 2019.

Research and development expenses were $41.2 million in the first quarter of 2020 as compared to $40.1 million in the same period in 2019. The increase in research and development expenses in the first quarter was primarily due to increased external expenses related to our clinical and preclinical activities, including our HD programs and C9orf72 program for ALS and FTD, and separation costs associated with the workforce reduction implemented in February 2020, partially offset by decreased external expenses related to our DMD programs due to our December 2019 decision to discontinue the suvodirsen program and to cease development of our other DMD programs.

General and administrative expenses were $13.0 million in the first quarter of 2020 as compared to $10.9 million in the same period in 2019. The increase in general and administrative expenses in the first quarter of 2020 was mainly driven by separation costs associated with the workforce reduction implemented in February 2020.

As of March 31, 2020, Wave had $120.9 million in cash and cash equivalents as compared to $147.2 million as of December 31, 2019. The decrease in cash and cash equivalents was mainly due to Wave's year-to-date net loss of $47.5 million, partially offset by the receipt of $20 million in research support funding from Takeda under our collaboration.

Wave expects that its existing cash and cash equivalents, together with expected and committed cash from its existing collaboration, 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 8:30 a.m. ET to discuss the company's first quarter 2020 operating results and provide a business update. The conference call may be accessed by dialing (866) 220-8068 (domestic) or +1 (470) 495-9153 (international) and entering conference ID 5669348. The live webcast may be accessed from the investor relations section of the Wave Life Sciences corporate website at www.ir.wavelifesciences.com. Following the webcast, a replay will be available on the website.

About PRISM™

PRISM is Wave Life Sciences' proprietary discovery and drug development platform that enables genetically defined diseases to be targeted with stereopure oligonucleotides across multiple therapeutic modalities. PRISM combines the company's unique ability to construct stereopure oligonucleotides with a deep understanding of how the interplay among oligonucleotide sequence, chemistry and backbone stereochemistry impacts key pharmacological properties. By exploring these interactions through iterative analysis of *in vitro* and *in vivo* outcomes and artificial intelligence-driven predictive modeling, the company continues to define design principles that are deployed across programs to rapidly develop and manufacture clinical candidates that meet pre-defined product profiles.

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: the anticipated commencement, patient enrollment, data readouts and completion of our clinical trials, and the announcement of such events; the protocol, design and endpoints of our ongoing and planned clinical trials; the future performance and results of our programs in clinical trials; future preclinical activities and programs; regulatory submissions; the progress and potential benefits of our collaborations with partners; the potential of our in vitro and in vivo preclinical data to predict the behavior of our compounds in humans; our identification of

future candidates and their therapeutic potential; the anticipated therapeutic benefits of our potential therapies compared to others; our ability to design compounds using multiple modalities and the anticipated benefits of that model; the anticipated benefits of our proprietary manufacturing processes and our internal manufacturing capabilities; the potential benefits of PRISM and our stereopure oligonucleotides compared with stereorandom oligonucleotides; the benefit of nucleic acid therapeutics generally; the strength of our intellectual property; 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 maintain the company infrastructure and personnel needed to achieve our goals; the impact of the COVID-19 global pandemic on our business 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 interactions; 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 our 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 indications, 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.

WAVE LIFE SCIENCES LTD.
UNAUDITED CONSOLIDATED BALANCE SHEETS

(In thousands, except share amounts)

	March 31, 2020	December 31, 2019
Assets		
Current assets:		
Cash and cash equivalents	$ 120,949	$ 147,161
Current portion of accounts receivable	—	20,000
Prepaid expenses	9,999	9,626
Other current assets	18,843	8,689
Total current assets	149,791	185,476
Long-term assets:		
Accounts receivable, net of current portion	30,000	30,000
Property and equipment, net	34,986	36,368
Operating lease right-of-use assets	17,659	18,101
Restricted cash	3,649	3,647
Other assets	2,487	10,658
Total long-term assets	88,781	98,774
Total assets	$ 238,572	$ 284,250
Liabilities, Series A preferred shares and shareholders' equity		
Current liabilities:		
Accounts payable	$ 16,486	$ 9,073
Accrued expenses and other current liabilities	10,994	16,185
Current portion of deferred revenue	88,044	89,652
Current portion of operating lease liability	3,357	3,243
Total current liabilities	118,881	118,153
Long-term liabilities:		
Deferred revenue, net of current portion	60,913	63,466
Operating lease liability, net of current portion	28,425	29,304
Other liabilities	1,621	1,721
Total long-term liabilities	$ 90,959	$ 94,491
Total liabilities	$ 209,840	$ 212,644
Series A preferred shares, no par value; 3,901,348 shares issued and outstanding at March 31, 2020 and December 31, 2019	$ 7,874	$ 7,874
Shareholders' equity:		
Ordinary shares, no par value; 34,601,582 and 34,340,690 shares issued and outstanding at March 31, 2020 and December 31, 2019, respectively	$ 540,161	$ 539,547
Additional paid-in capital	61,276	57,277
Accumulated other comprehensive income	273	267
Accumulated deficit	(580,852)	(533,359)
Total shareholders' equity	$ 20,858	$ 63,732
Total liabilities, Series A preferred shares and shareholders' equity	$ 238,572	$ 284,250

The accompanying notes are an integral part of the unaudited consolidated financial statements.

WAVE LIFE SCIENCES LTD.
UNAUDITED CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

(In thousands, except share and per share amounts)

	Three Months Ended March 31,	
	2020	2019
Revenue	$ 4,161	$ 3,026
Operating expenses:		
Research and development	41,158	40,113
General and administrative	12,996	10,901
Total operating expenses	54,154	51,014
Loss from operations	(49,993)	(47,988)
Other income, net:		
Dividend income	385	1,424
Interest income, net	3	11
Other income (expense), net	2,112	2,353
Total other income, net	2,500	3,788
Loss before income taxes	(47,493)	(44,200)
Income tax provision	—	—
Net loss	$ (47,493)	$ (44,200)
Net loss per share attributable to ordinary shareholders—basic and diluted	$ (1.38)	$ (1.36)
Weighted-average ordinary shares used in computing net loss per share attributable to ordinary shareholders—basic and diluted	34,461,505	32,597,158
Other comprehensive income (loss):		
Net loss	$ (47,493)	$ (44,200)
Foreign currency translation	6	97
Comprehensive loss	$ (47,487)	$ (44,103)

The accompanying notes are an integral part of the unaudited consolidated financial statements.

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Exhibit 99.2

Wave Life Sciences

Corporate Presentation

May 11, 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.

WAVE
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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

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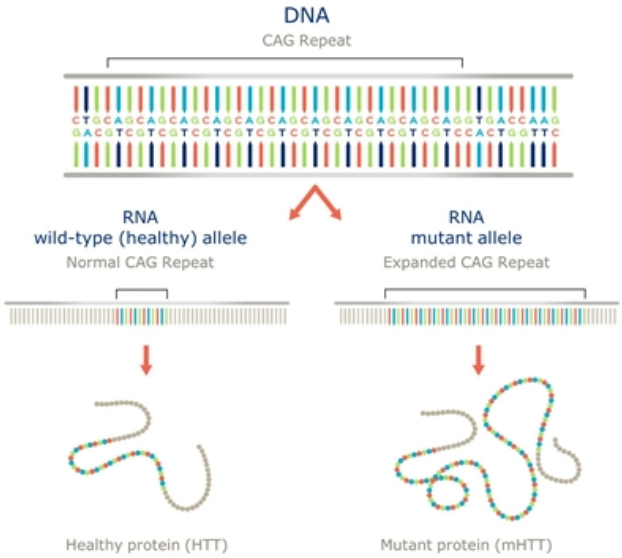
*Estimates of U.S. prevalence and addressable population by target based on publicly available data and are approximate; for Huntington's disease, numbers approximate manifest and pre-manifest populations, respectively.
†During a four-year term, Wave and Takeda may collaborate on up to six preclinical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

WAVE™
LIFE SCIENCES

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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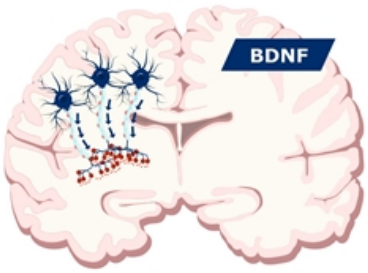
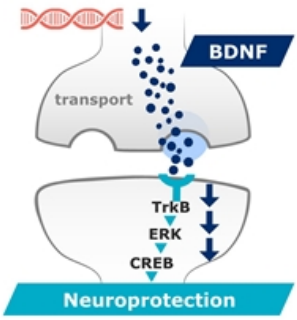
Importance of wild-type huntingtin (wtHTT) in HD

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

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
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Check for updates

Gunnar H. D. Poplawski[1,2], Riki Kawaguchi[3,4], Erna Van Niekerk[1], Paul Lu[1,4], Neil Mehta[1], Philip Canete[1], Richard Lie[1], Ioannis Dragatsis[5], Jessica M. Meves[1], Binhai Zheng[3,4], Giovanni Coppola[3,6] & Mark H. Tuszynski[1,4,7]

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

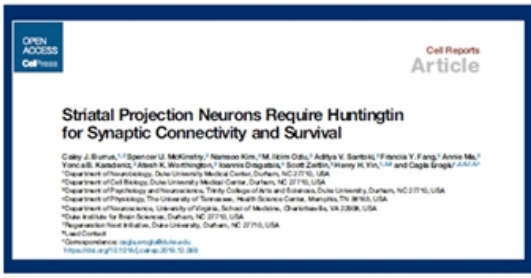
Recent publications on wtHTT LoF as a likely driver of HD pathogenesis


Neurobiology of Disease

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, Andrew Morton, Sarah L. Gordon, Julia F. Alterman, Anastasia Khvorova, Michael A. Cousin, Karen J. Smillie

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


Cell Reports
Article

Striatal Projection Neurons Require Huntingtin for Synaptic Connectivity and Survival

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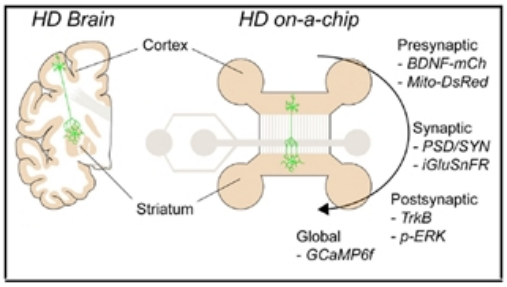
LoF: Loss of function; wtHTT: wild-type huntingtin; HD: Huntington's disease; STN: subthalamic nucleus

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

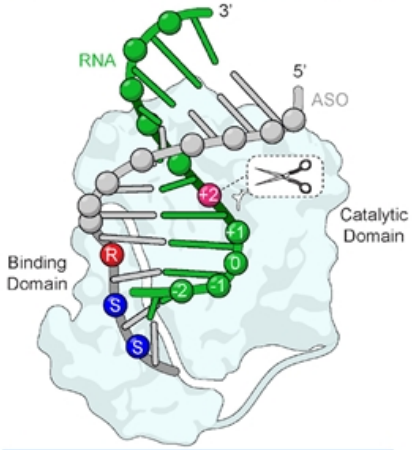
WAVE LIFE SCIENCES

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



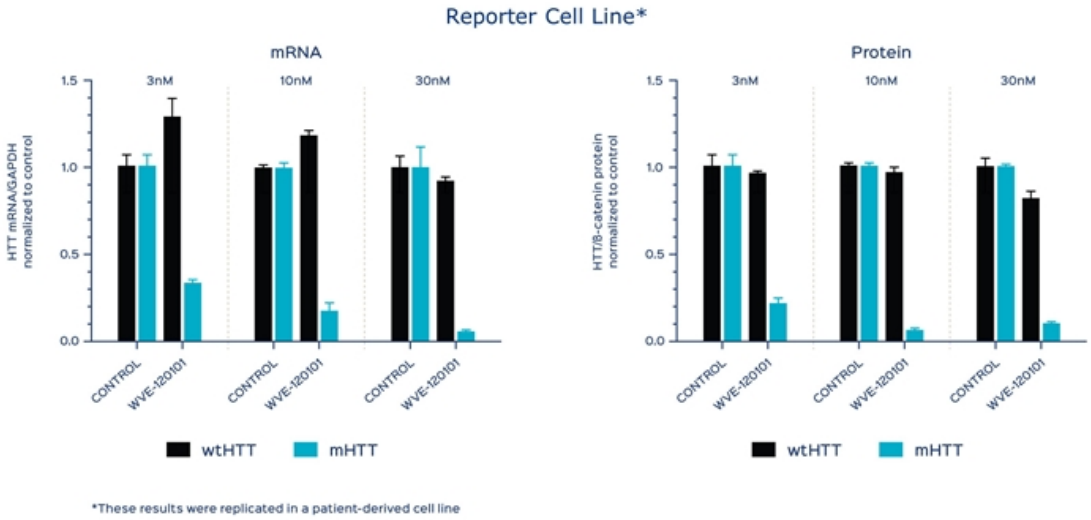
RNase H and ASO:RNA

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

WAVE LIFE SCIENCES

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

Selective reduction of mHTT mRNA & protein



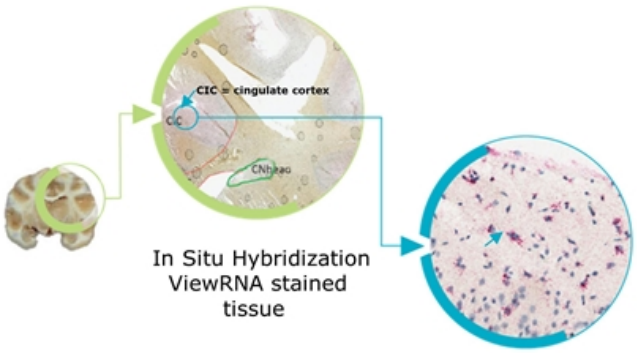
*These results were replicated in a patient-derived cell line

WAVE LIFE SCIENCES

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

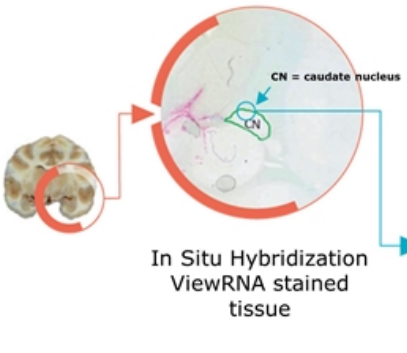
- WVE-120101 and WVE-120102 distribution in cynomolgus non-human primate brain following intrathecal bolus injection



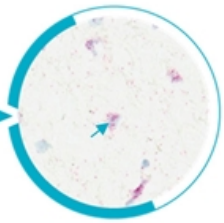
In Situ Hybridization ViewRNA stained tissue

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

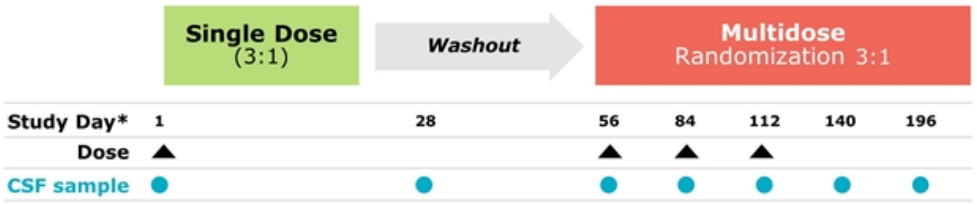
Arrow points to nuclear and perinuclear distribution of WVE-120102 in caudate nucleus

WAVE LIFE SCIENCES

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 trial design

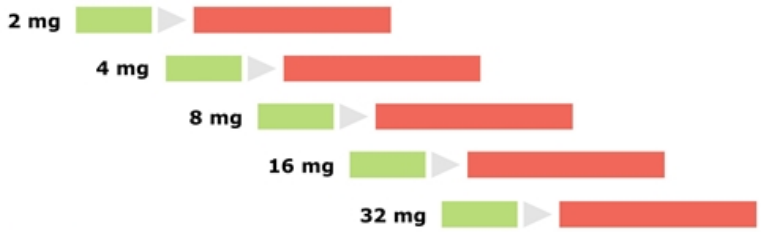
Two parallel, multicenter, double-blind, randomized, placebo-controlled Phase 1b/2a clinical trials for WVE-120101 and WVE-120102



PRECISION-HD2 OLE:
Initiated October 2019

PRECISION-HD1 OLE:
Initiated February 2020

Multidose Cohorts
N = 12 per cohort



- PRECISION-HD2 data from 32 mg cohort expected in 2H 2020
- PRECISION-HD1 topline data, including 32 mg cohort, expected 2H 2020

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OLE: Open label extension; CSF: cerebrospinal fluid *Study day may vary depending on patient washout period

PRECISION-HD2 topline results

Clinical trial ongoing

Doses	Safety	Biomarker Effects	
		mHTT	wtHTT
• **WVE-120102 2–16 mg (pooled)**	• **Generally safe and well tolerated**	• **Reduction in mHTT compared to placebo (-12.4%[1], p<0.05[2])** • **Analysis across groups suggests dose response at highest doses (p=0.03)[3]**	• **No change in tHTT compared to placebo** • **Ongoing evaluation**
• 32 mg cohort initiated • Assessing the potential for higher dose cohorts	• Safety profile supports addition of higher dose cohorts	• Potential for greater mHTT reduction at higher doses	• Larger reductions of mHTT expected to result in discernible impact on tHTT

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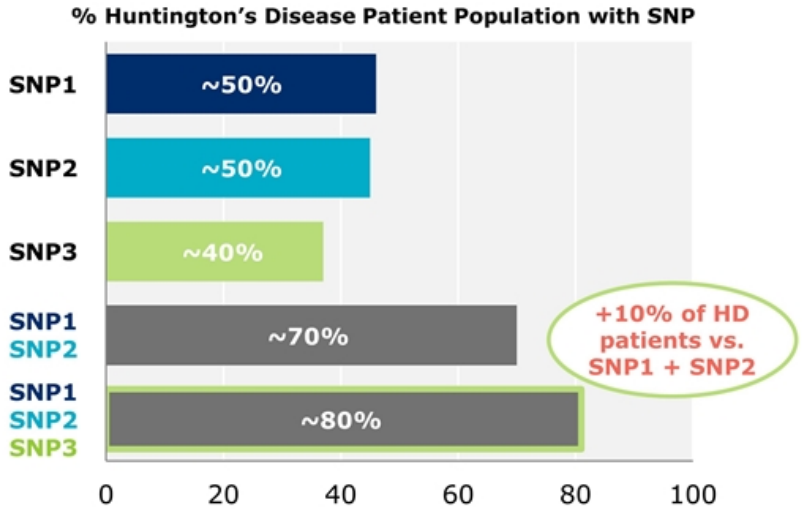
Topline results announced December 30. 2019; mHTT: mutant huntingtin wtHTT: wild-type HTT tHTT: total HTT
[1] Hodges-Lehmann non-parametric shift estimates of the difference between treatment and placebo; [2] Wilcoxon-Mann-Whitney non-parametric significance test; [3] Multiple Contrast Test (MCT)

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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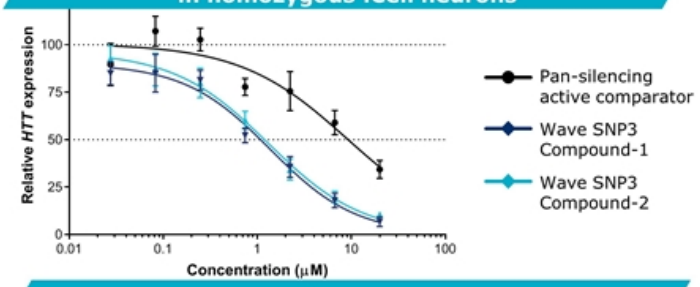
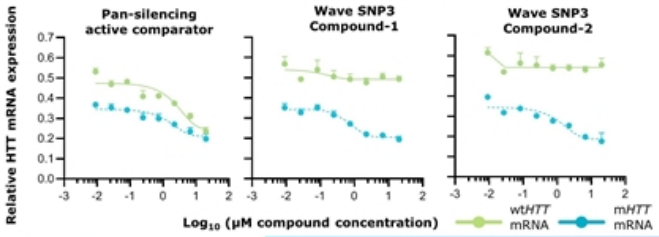
SNP3 program approaching clinical development

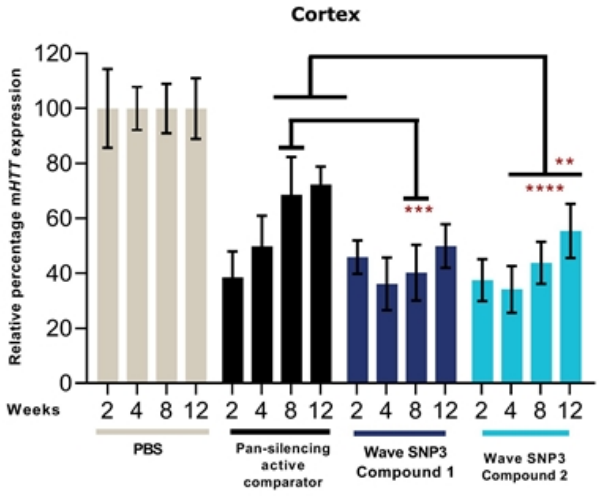
Potent mutant *HTT* knockdown activity in homozygous iCell neurons



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

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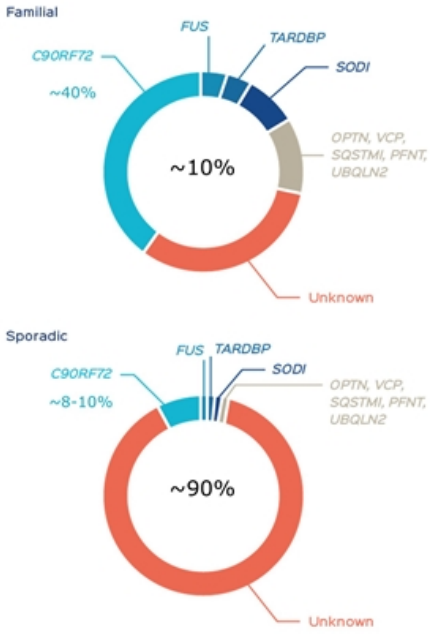
Source: DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. *Neuron.* 2011;72:245-256. Renton AE, Majounie E, Waite A, et al. *Neuron.* 2011;72:257-268.

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

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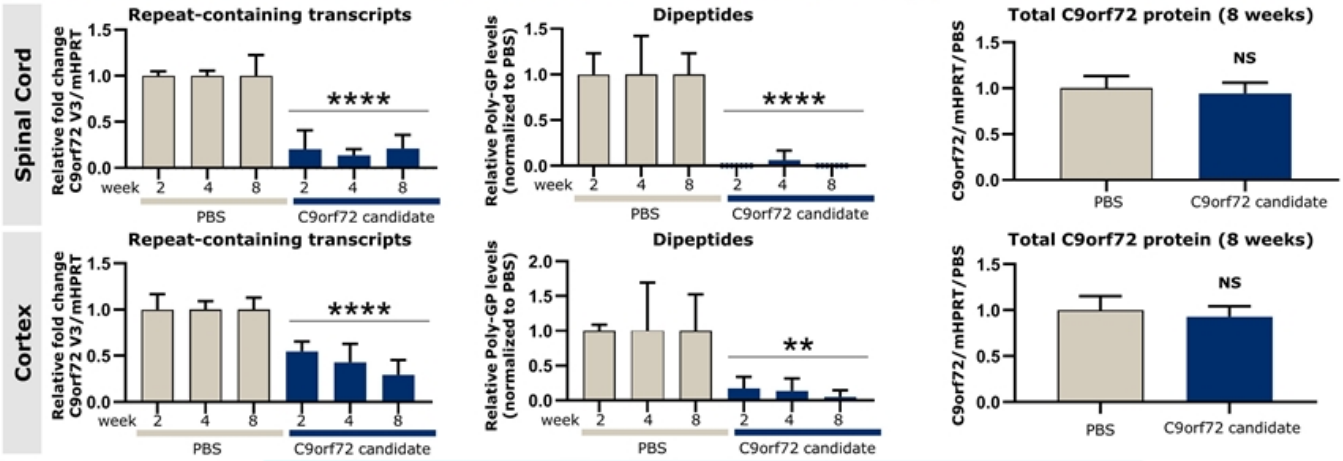
Sources: Stevens M, et al. Familial aggregation in frontotemporal dementia. *Neurology*. 1998;50:1541-1545. Majounie E, et al. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. *Lancet Neurol.*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

C9orf72 program: 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



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.

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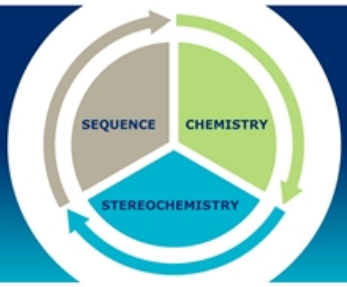
PRISM Platform

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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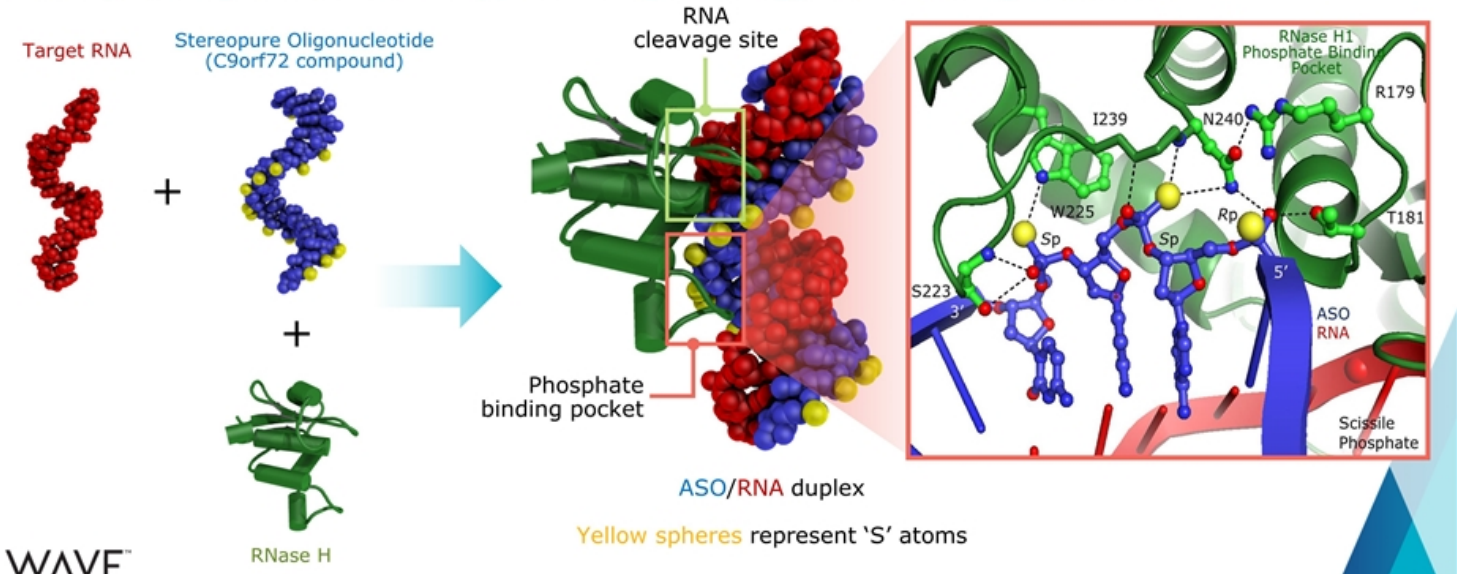
PRISM enables optimal placement of backbone stereochemistry

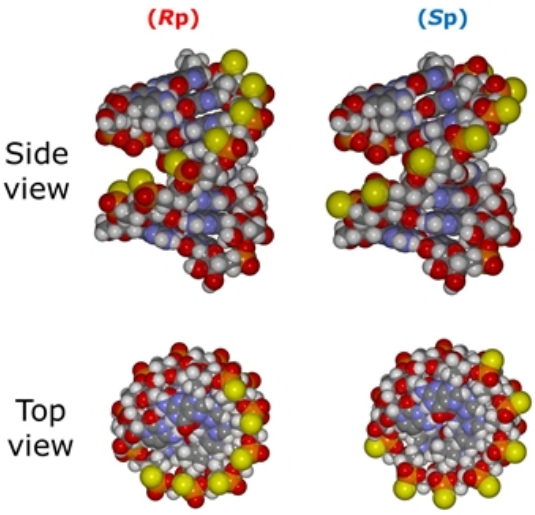
Crystal structure confirms phosphate-binding pocket of RNase H binds 3′-SSR-5′ motif in stereopure oligonucleotide – supports design strategy for Wave oligonucleotides



Yellow spheres represent 'S' atoms

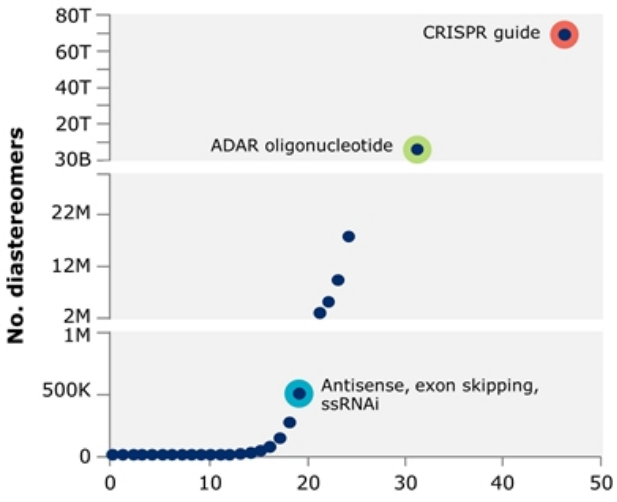
Importance of controlling stereochemistry

Stereochemical diversity



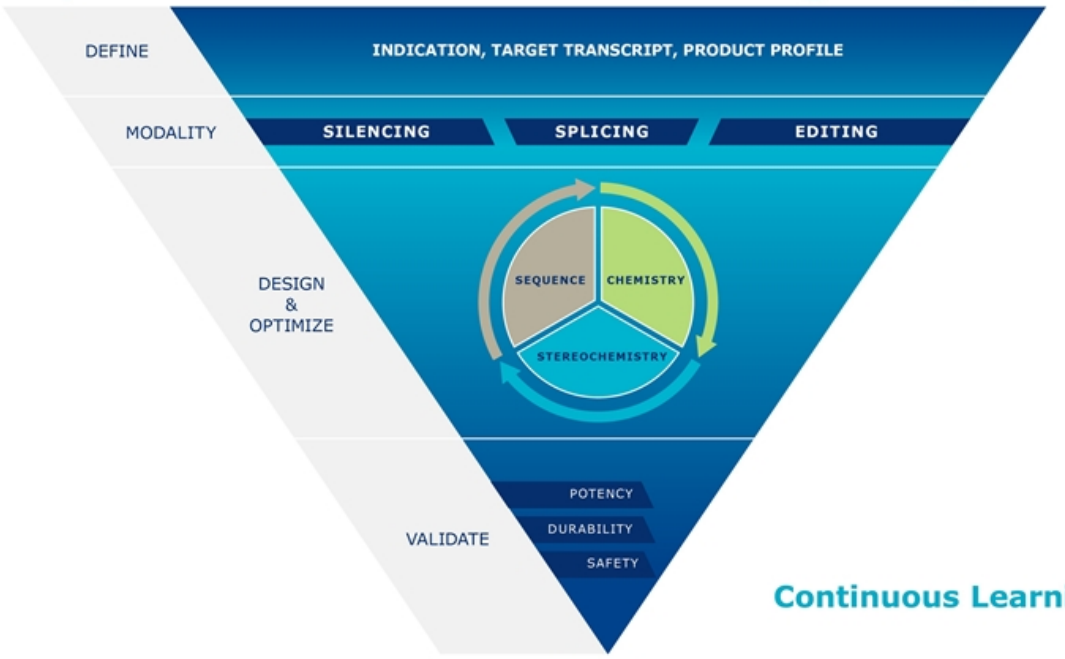
WAVE LIFE SCIENCES Yellow spheres represent 'S' atoms PS: Phosphorothioate

Exponential diversity arises from uncontrolled stereochemistry



Number of PS linkages in oligonucleotide backbone

PRISM platform enables rational drug design



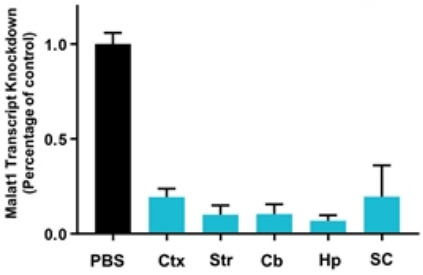
Continuous Learning

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

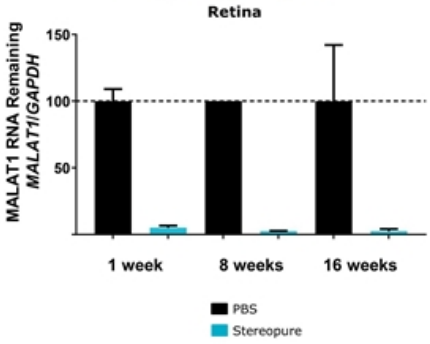
CNS

Malat1 Transcript Knockdown in Mice
10 Weeks after single 100 µg ICV injection



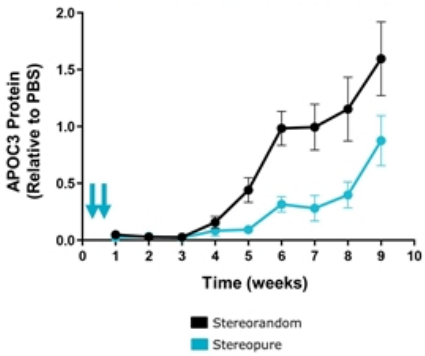
Eye

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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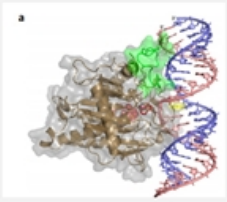
ADAR-mediated RNA editing

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)

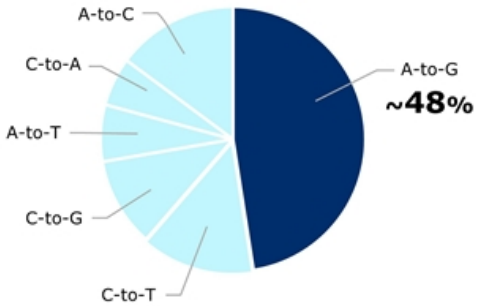


- Endogenous proteins that catalyze A-to-I RNA editing
- Upon translation, I recognized as G, leading to A-to-G editing

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]

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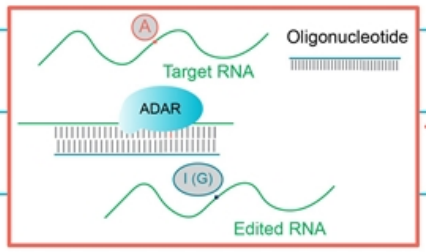
SNP: single nucleotide polymorphism A: Adenosine I: Inosine G: Guanosine
[1] Gaudeli NM et al. *Nature* (2017). [2] ClinVar database

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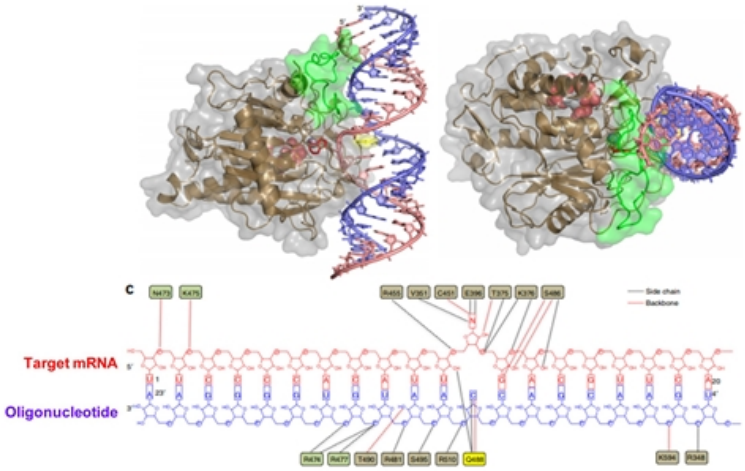
I (G): ADAR converts A>I, I is recognized as G by all cellular machinery; ADAR: Adenosine Deaminase Acting on RNA; ORF: Open reading frame

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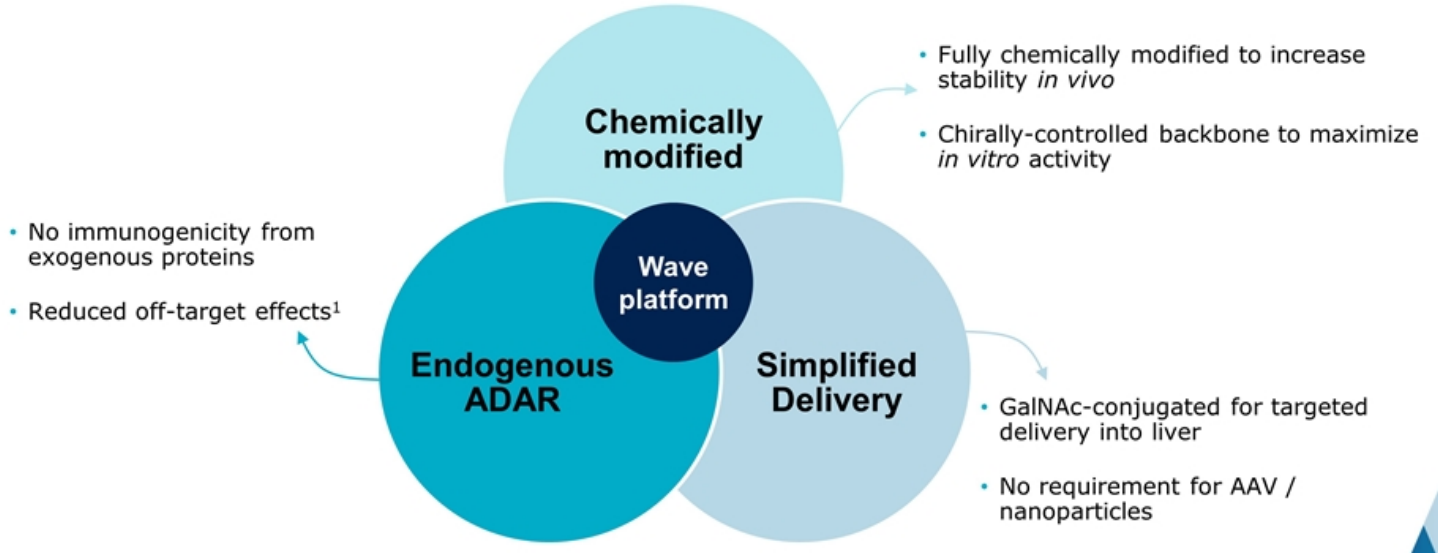
Structure adapted from Matthews et al., Nat Struct Mol Biol. (2016); SAR = structure-activity relationship; ADAR: Adenosine Deaminase Acting on RNA; dsRNA = double-stranded RNA

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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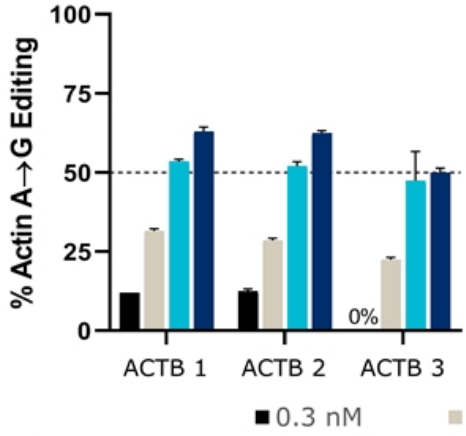
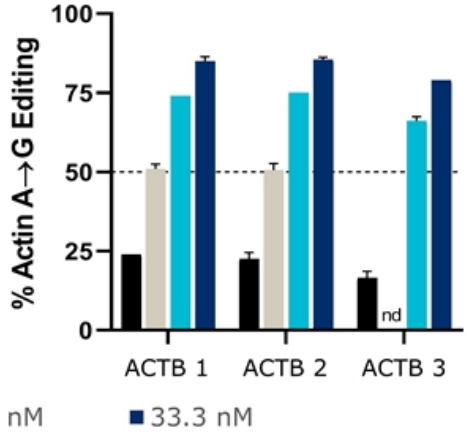
[1]Chen et al. Biochemistry 2019

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

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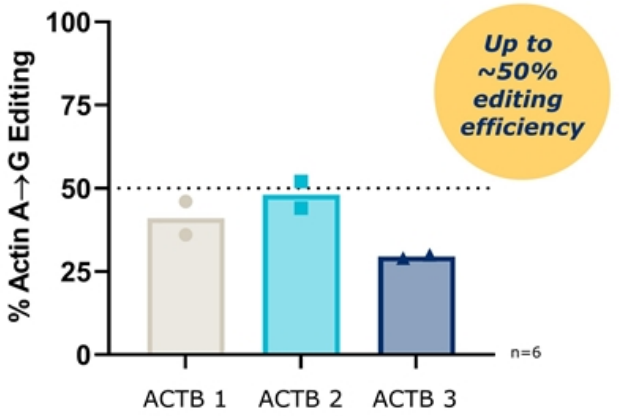
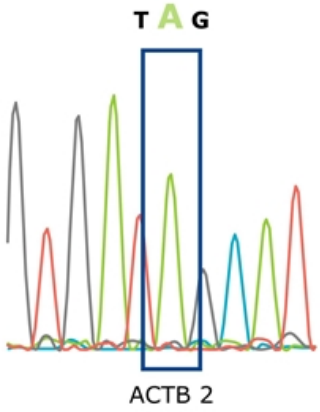
NHP: non-human primate; ACTB: Beta-actin; nd= not determined
Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR.

First non-human primate RNA editing

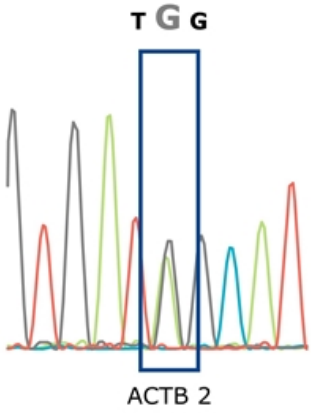
In vivo – NHP



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

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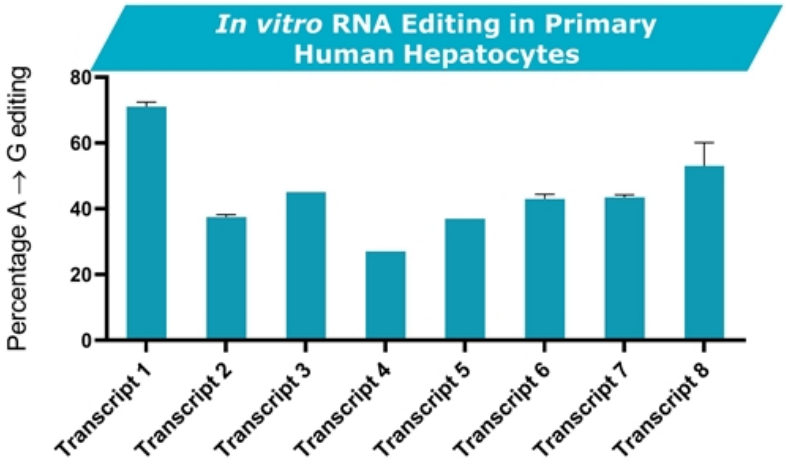
NHP – non-human primate; ACTB: Beta-actin; Left: 5mg/kg SC: Day 1,2,3,4,5; Liver Biopsy for mRNA (ACTB Editing) & eASO Exposure: Day 7 Right: % Editing quantified from Sanger sequencing using EditR program.

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

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Ophthalmology

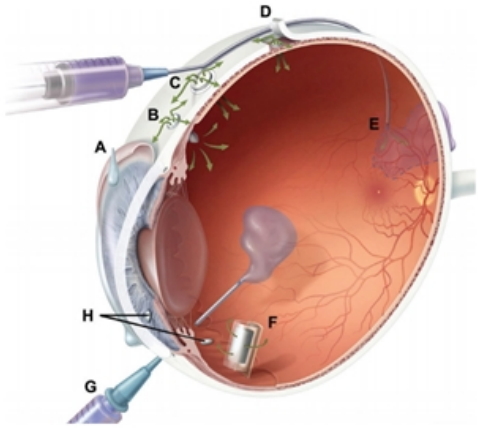
Stereopure oligonucleotides for inherited retinal diseases (IRDs)

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



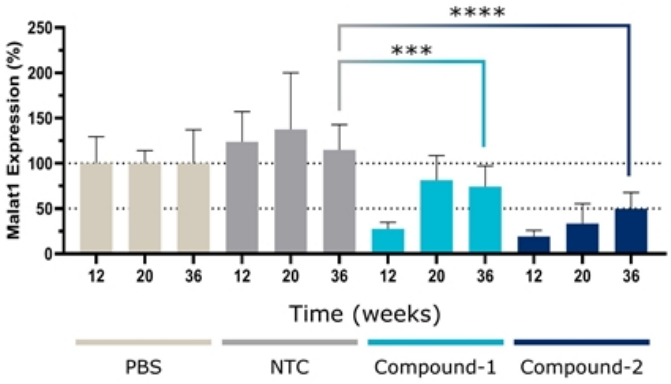
Intravitreal injection

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

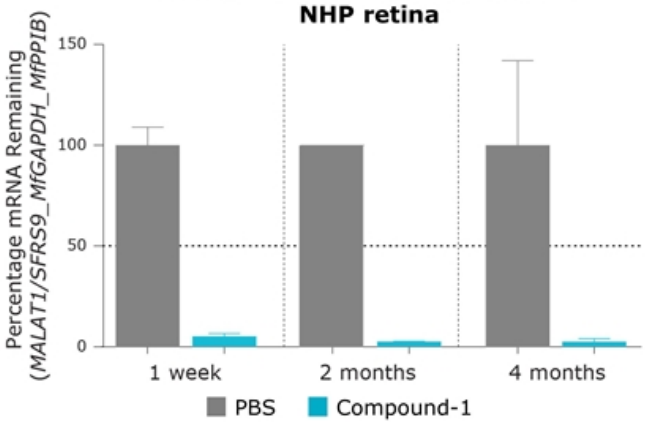
~50% *MALAT1* knockdown at 9 months

***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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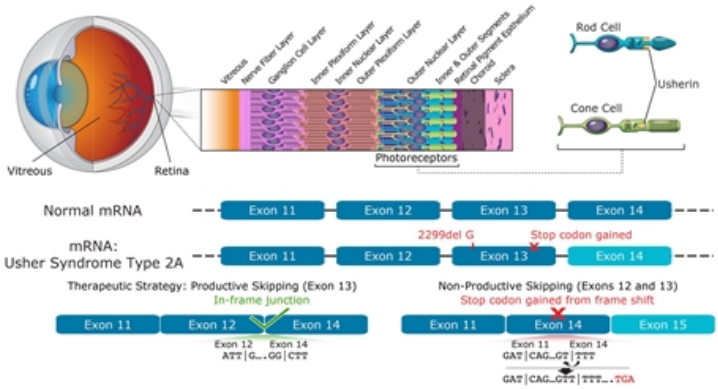
Mouse: Compound or PBS (1 x 50 mg IVT) was delivered to C57BL6 mice. Relative percentage of Malat1 RNA in the posterior of the eye (retina, choroid, sclera) to PBS-treated mice is shown at 12, 20 and 36 weeks post-single injection. Statistics: Compound-2 Malat1 levels are significantly different from 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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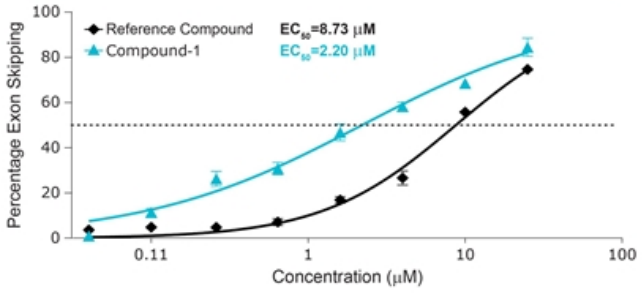
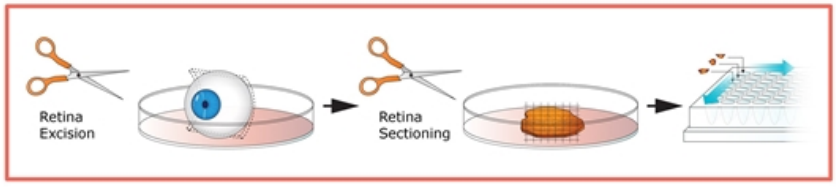
Sources: Boughman et al., 1983. *J Chron Dis.* 36:595-603; Seyedahmadi et al., 2004. *Exp Eye Res.* 79:167-173; Liu et al., 2007. *Proc Natl Acad Sci USA* 104:4413-4418.

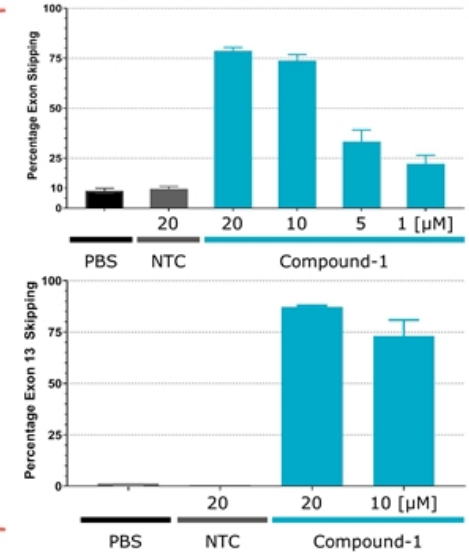
Potent USH2A exon 13 skipping with stereopure compound in *vitro* and *ex vivo*

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





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

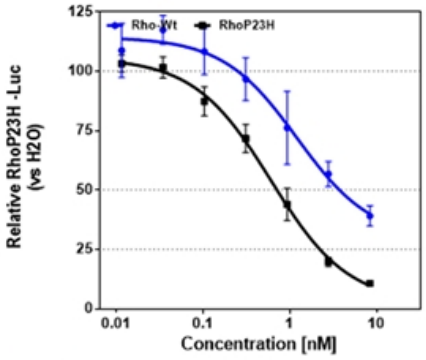


Left: Compounds were added to Y79 cells under free-uptake conditions. Exon skipping was evaluated by Taqman assays. *USH2A* transcripts were normalized to *SRSF9*. Data are mean±s.d., n=2. Reference Compound: van Diepen *et al.* 2018. Antisense oligonucleotides for the treatment of eye disease. W020180551134A1. 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.

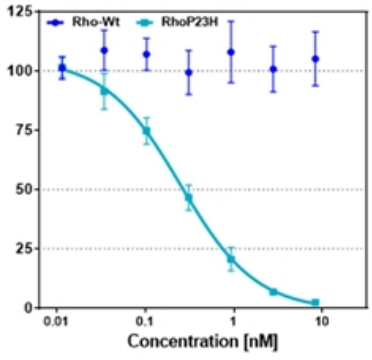
Allele-selective reduction of SNP-containing allele for adRP associated with Rhodopsin P23H mutation

- **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

- **2H 2020:** PRECISION-HD2 data from 32 mg cohort in Huntington's disease
- **2H 2020:** PRECISION-HD1 topline data, including 32 mg cohort, in Huntington's disease
- **2H 2020:** Initiate clinical development of SNP3 program in Huntington's disease
- **2H 2020:** Initiate clinical development of C9orf72 program in ALS and FTD

Ophthalmology

- **2020:** Advance USH2A and RhoP23H programs

Hepatic

- ✓ **2020:** *In vivo* ADAR editing data
- **2020:** Additional *in vivo* ADAR-mediated RNA-editing data and announce first RNA-editing program

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Realizing the potential of genetic medicines

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