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 13, 2021

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))

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. ☐

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**

Item 2.02 Results of Operations and Financial Condition.

On May 13, 2021, Wave Life Sciences Ltd. (the "Company") announced its financial results for the quarter ended March 31, 2021. 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 13, 2021, 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 are being furnished and 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 they be deemed incorporated by reference into any registration statement or other filing under the Securities Act of 1933, as amended, or the Exchange Act, except as shall be expressly set forth by specific reference in such 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 13, 2021
99.2	Corporate Presentation of Wave Life Sciences Ltd. dated May 13, 2021
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 13, 2021

Wave Life Sciences Reports First Quarter 2021 Financial Results and Provides Business Update

Clinical trials underway with next-generation candidates incorporating PN chemistry

Clinical data from PN chemistry programs expected in 2022

In vivo ADAR editing data for AATD program on track for 1H 2021

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

CAMBRIDGE, Mass., May 13, 2021 (GLOBE NEWSWIRE) — 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, 2021 and provided a business update.

“Despite our PRECISION-HD results at the end of the first quarter, it has been a productive start of the year for Wave and our team remains focused on advancing our clinical trials for ALS/FTD, HD and DMD. These new trials mark the transition of our next-generation programs into the clinic. We expect clinical data that will provide insight into PN chemistry and enable decision making on next steps for these programs next year,” said Paul Bolno, MD, MBA, President and Chief Executive Officer of Wave Life Sciences. “We have a deep and diverse pipeline of RNA therapeutics, each designed with our PN chemistry, which has been shown to increase potency, exposure and durability compared to our first-generation compounds in preclinical studies. We continue to produce compelling *in vivo* data, and we are advancing multiple programs for CNS indications, including Alzheimer’s disease, Parkinson’s disease and others, in collaboration with our partner Takeda. Our ADAR editing capability demonstrates the diversity of our genetic medicines toolkit and we are well-positioned to be leaders in the RNA editing field. We look forward to providing more updates on ADAR editing, including the first *in vivo* data from our AATD program, in the first half of this year.”

Recent Business Highlights and Upcoming Milestones

WVE-004 (C9orf72) for amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD):

- WVE-004 is an investigational antisense oligonucleotide designed to selectively target transcript variants containing a hexanucleotide repeat expansion (G_4C_2) in the C9orf72 gene, which is one of the most common genetic causes of the sporadic and inherited forms of ALS and FTD. WVE-004 uses novel PN backbone chemistry modifications.
- In February 2021, Wave published in *Nature Communications* the results of initial work to identify and validate its targeting strategy to achieve variant-selective knockdown of expansion-containing C9orf72 transcripts.
- In April 2021, during a platform presentation at the American Academy of Neurology (AAN) 2021 Virtual Annual Meeting, Wave highlighted preclinical *in vivo* data for WVE-004, which demonstrated potent and durable knockdown of more than 90% of polyGP dipeptide repeat (DPR) proteins in the spinal cord and at least 80% in the cortex, an effect that persisted for at least six months. C9orf72 protein was relatively unchanged over the same time period.

- This week, at the European Network to Cure ALS (ENCALS) meeting being held May 12 – May 14, Wave is presenting a poster introducing its FOCUS-C9 Phase 1b/2a trial design for WVE-004. The FOCUS-C9 trial is a global, multicenter, randomized, double-blind, placebo-controlled Phase 1b/2a clinical trial to assess the safety and tolerability of intrathecal doses of WVE-004 for patients with C9-ALS and/or C9-FTD. Additional objectives include measurement of polyGP proteins in the cerebrospinal fluid (CSF), plasma and CSF pharmacokinetics, and exploratory biomarker and clinical endpoints. The FOCUS-C9 trial is designed to be adaptive and includes single- and multiple-ascending dose portions, with dose escalation and dosing frequency being guided by an independent safety committee.
- Wave has received regulatory and ethics approvals and site activation is underway for the FOCUS-C9 clinical trial, and Wave expects to initiate dosing in 2021.

WVE-003 (SNP3) for Huntington's disease (HD):

- WVE-003 is Wave's next-generation HD candidate and Wave's first HD candidate that uses PN chemistry. WVE-003 is designed to selectively target the mutant allele of the *huntingtin* (mHTT) gene, while leaving the wild-type (wtHTT) protein relatively intact. Wave's approach to HD is guided by the recognition that, in addition to a gain of function of the mHTT protein, people with this disease have less wtHTT protein, leaving them with a smaller protective reservoir of healthy protein than unaffected individuals. A growing body of scientific evidence suggests that preserving as much of this essential protein as possible, when in the setting of stress from toxic mHTT protein, may be important for favorable clinical outcomes.
- In April 2021, at the 16th Annual CHDI Foundation Huntington's Disease Therapeutic Conference, Wave highlighted preclinical data for WVE-003, which showed selective reduction of mHTT mRNA *in vitro* and potent and durable knockdown of mHTT mRNA *in vivo*. Wave also introduced the design for the Phase 1b/2a clinical trial of WVE-003, called SELECT-HD. The multicenter, randomized, double-blind, placebo-controlled trial will assess the safety and tolerability of intrathecally administered WVE-003 for patients with early manifest Huntington's disease. Additional objectives include measurement of mHTT and wtHTT protein and exploratory pharmacokinetic, pharmacodynamic, clinical and MRI endpoints. The trial is designed to be adaptive, with dose escalation and dosing frequency being guided by an independent safety committee.
- Wave has received regulatory and ethics approvals and site activation is underway for the SELECT-HD clinical trial, and Wave expects to initiate dosing in 2021.

WVE-N531 for Duchenne muscular dystrophy (DMD) amenable to exon 53 skipping:

- WVE-N531 is Wave's first splicing candidate to incorporate PN chemistry, which Wave advanced following results of an *in vivo* study in double knock-out mice (dKO) that showed that an oligonucleotide designed with PN chemistry appeared to significantly increase dystrophin production and substantially improve survival, compared to oligonucleotides designed with Wave's first-generation chemistry.
- In March 2021, Wave initiated clinical development of WVE-N531 with the submission of a clinical trial application.
- Wave has received regulatory approval for a clinical trial of WVE-N531 to assess initial safety and dystrophin production in patients with DMD amenable to exon 53 skipping. Wave expects to initiate dosing in this trial in 2021.

ADAR editing:

- In March 2021, Wave presented a poster at the 2021 Keystone eSymposia on Precision Engineering of the Genome, Epigenome and Transcriptome highlighting the breadth of RNA editing data generated using its ADAR editing capability to date. This presentation illustrated editing activity across *in vivo* and *in vitro* systems, including *in vivo* editing in the CNS, using conjugated and non-conjugated oligonucleotides. Wave will also present these data in an oral presentation at the 24th American Society of Gene and Cell Therapy (ASGCT) Annual Meeting being held this week, May 11 – 14, 2021.
- Wave expects to present additional ADAR editing data at scientific congresses in 2021.

Alpha-1 antitrypsin deficiency (AATD) program with ADAR editing:

- Wave's AATD program, its first ADAR editing program, uses an oligonucleotide to correct the single RNA base mutation in mRNA coded by the *SERPINA1* Z allele. ADAR editing may provide an ideal approach to treating AATD by increasing circulating levels of healthy alpha-1 antitrypsin (AAT) protein and reducing aggregation in the liver, thus simultaneously addressing both the lung and liver manifestations of the disease.
- To support the continued development of its AATD program, Wave has developed a proprietary humanized SERPINA1/ADAR model. Wave expects to share *in vivo* data from this model in the first half of 2021 and plans to submit these data for presentation at a scientific congress in 2021.

First Quarter 2021 Financial Results and Financial Guidance

Wave reported a net loss of $42.5 million in the first quarter of 2021 as compared to $47.5 million in the same period in 2020.

Research and development expenses were $33.4 million in the first quarter of 2021 as compared to $41.2 million in the same period in 2020. The year-over-year decrease was primarily due to the decrease in external expenses related to Wave's suvodirsen program, which was discontinued in December 2019, but had wind-down costs throughout 2020, as well as decreases in compensation-related expenses and other external expenses, partially offset by the increases in external expenses related to Wave's clinical and preclinical activities related to its HD programs and its *C9orf72* program for ALS and FTD.

General and administrative expenses were $10.1 million in the first quarter of 2021, as compared to $13.0 million in the same period in 2020. The year-over-year decrease was driven by decreases in compensation-related expenses and other external expenses.

Wave ended the first quarter of 2021 with $148.5 million in cash and cash equivalents, as compared to $184.5 million as of December 31, 2020. The decrease in cash and cash equivalents was mainly due to Wave's year-to-date net loss, partially offset by the receipt of $8.0 million in net proceeds under Wave's at-the-market equity program. In April 2021, Wave received an additional $30.0 million in committed research support under its collaboration with Takeda.

Wave expects that its existing cash and cash equivalents, together with expected and committed cash from its existing collaboration, will enable the company to fund its operating and capital expenditure requirements into the second quarter of 2023.

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 and 2021 financial results and provide a business update. The conference call may be accessed by dialing (866) 220-8068 (domestic) or (470) 495-9153 (international) and entering conference ID: 7430859. The live webcast may be accessed from the investor relations section of the Wave Life Sciences corporate website at 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, including silencing, splicing and editing. 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 machine learning-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 adaptive 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 product 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, including our novel PN backbone chemistry modifications, and our stereopure oligonucleotides compared with stereorandom oligonucleotides; the potential benefits of our novel ADAR-mediated RNA editing platform capabilities compared to others; the benefit of nucleic acid therapeutics generally; the strength of our intellectual property; the anticipated duration of our cash runway; and our expectations regarding the impact of the COVID-19 pandemic on our business. 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 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, including their receptiveness to our adaptive trial designs; our effectiveness in managing future clinical trials and regulatory interactions; the effectiveness of PRISM, including our novel PN backbone chemistry modifications ; the effectiveness of our novel ADAR-mediated RNA editing platform capability; 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; competition from others developing therapies for similar indications; the severity and duration of the COVID-19 pandemic and its negative impact on the conduct of, and the timing of enrollment, completion and reporting with respect to, our clinical trials; and any other impacts on our business as a result of or related to the COVID-19 pandemic, 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, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 148,535	$ 184,497
Current portion of accounts receivable	30,000	30,000
Prepaid expenses	10,430	10,434
Other current assets	5,580	5,111
Total current assets	194,545	230,042
Long-term assets:		
Property and equipment, net	27,370	29,198
Operating lease right-of-use assets	15,720	16,232
Restricted cash	3,651	3,651
Other assets	1,361	115
Total long-term assets	48,102	49,196
Total assets	$ 242,647	$ 279,238
Liabilities, Series A preferred shares and shareholders' equity		
Current liabilities:		
Accounts payable	$ 13,418	$ 13,795
Accrued expenses and other current liabilities	6,661	11,971
Current portion of deferred revenue	24,763	91,560
Current portion of operating lease liability	3,838	3,714
Total current liabilities	48,680	121,040
Long-term liabilities:		
Deferred revenue, net of current portion	108,278	41,481
Operating lease liability, net of current portion	24,587	25,591
Other liabilities	407	474
Total long-term liabilities	133,272	67,546
Total liabilities	$ 181,952	$ 188,586
Series A preferred shares, no par value; 3,901,348 shares issued and outstanding at March 31, 2021 and December 31, 2020	$ 7,874	$ 7,874
Shareholders' equity:		
Ordinary shares, no par value; 49,854,651 and 48,778,678 shares issued and outstanding at March 31, 2021 and December 31, 2020, respectively	$ 702,649	$ 694,085
Additional paid-in capital	75,636	71,573
Accumulated other comprehensive income	269	389
Accumulated deficit	(725,733)	(683,269)
Total shareholders' equity	$ 52,821	$ 82,778
Total liabilities, Series A preferred shares and shareholders' equity	$ 242,647	$ 279,238

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,	
	2021	2020
Revenue	$ —	$ 4,161
Operating expenses:		
Research and development	33,393	41,158
General and administrative	10,078	12,996
Total operating expenses	43,471	54,154
Loss from operations	(43,471)	(49,993)
Other income, net:		
Dividend income and interest income, net	11	388
Other income, net	996	2,112
Total other income, net	1,007	2,500
Loss before income taxes	(42,464)	(47,493)
Income tax provision	—	—
Net loss	$ (42,464)	$ (47,493)
Net loss per share attributable to ordinary shareholders—basic and diluted	$ (0.86)	$ (1.38)
Weighted-average ordinary shares used in computing net loss per share attributable to ordinary shareholders—basic and diluted	49,101,606	34,461,505
Other comprehensive income (loss):		
Net loss	$ (42,464)	$ (47,493)
Foreign currency translation	(120)	6
Comprehensive loss	$ (42,584)	$ (47,487)

Investor Contact:
Kate Rausch
617-949-4827
krausch@wavelifesci.com

Media Contact:
Alicia Suter
617-949-4817
asuter@wavelifesci.com

Exhibit 99.2

WAVE™
LIFE SCIENCES

Wave Life Sciences

Corporate Presentation

May 13, 2021

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
LIFE SCIENCES

Building a leading genetic medicines company

INNOVATIVE PLATFORM

- Stereopure oligonucleotides
- Novel backbone modifications (PN chemistry)
- Allele-selectivity
- Multiple modalities (silencing, splicing, ADAR editing)
- Strong IP position[1]

FOUNDATION OF NEUROLOGY PROGRAMS

- ALS / FTD
- Huntington's disease
- Neuromuscular diseases
- Ataxias
- Parkinson's disease
- Alzheimer's disease

PRISM
Wave's discovery and drug development platform

CLINICAL DEVELOPMENT EXPERTISE

- Multiple global clinical trials
- Innovative trial designs

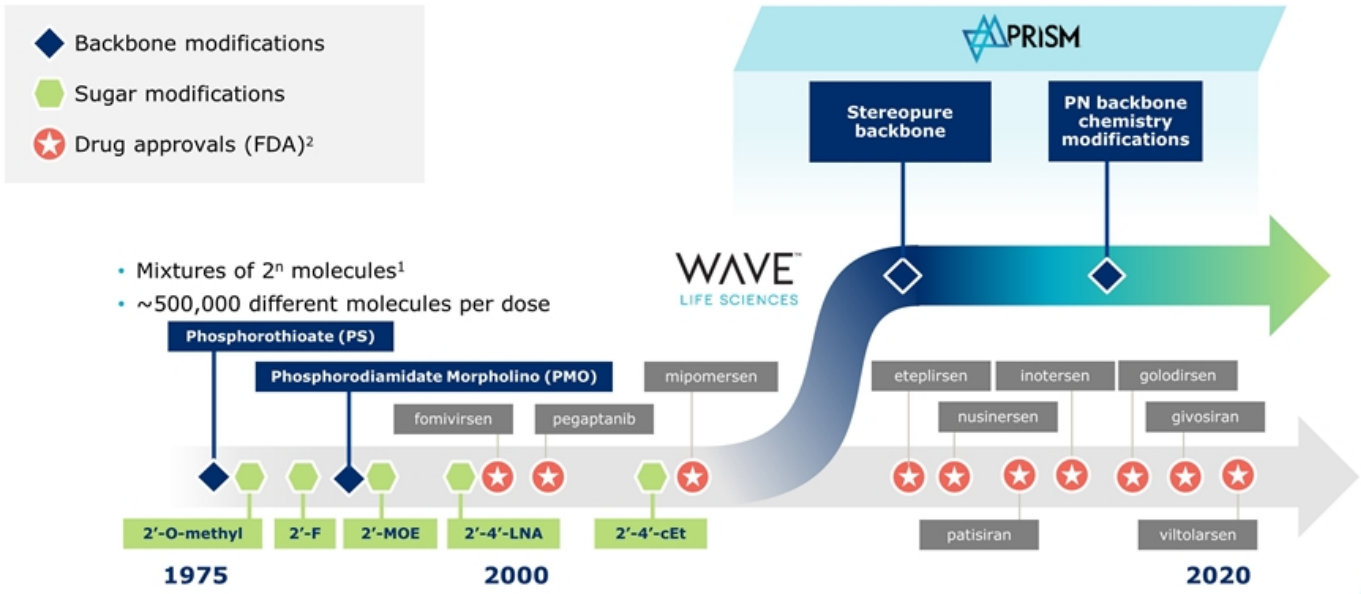
MANUFACTURING

- Established internal manufacturing capabilities to produce oligonucleotides at scale

WAVE LIFE SCIENCES

ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia
[1]stereopure oligonucleotides and novel backbone chemistry modifications

PRISM has unlocked novel and proprietary advances in oligonucleotide design

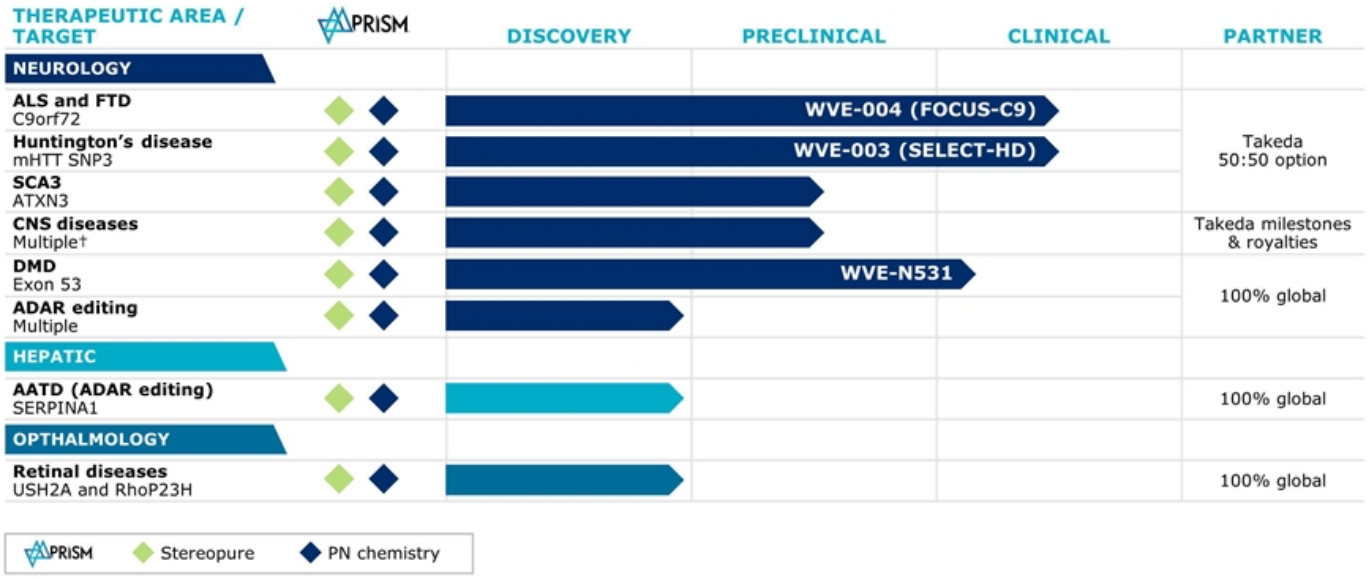


WAVE LIFE SCIENCES

[1]n=number of chiral centers

[2]oligonucleotide therapies approved by the FDA across the industry

Innovative pipeline led by neurology programs



WAVE LIFE SCIENCES

†During a four-year term, Wave and Takeda may collaborate on up to six preclinical targets at any one time.
ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; SCA3: Spinocerebellar ataxia 3; CNS: Central nervous system;
DMD: Duchenne muscular dystrophy; AATD: Alpha-1 antitrypsin deficiency

Platform evolution reflected in clinical pipeline

Oligonucleotide innovation and optimization
- PN backbone chemistry modifications
- Interactions between sequence, chemistry and stereochemistry

***In vivo* models**
- Insight into PK / PD relationships
- Novel model generation

Leverage learnings of first generation programs
- Translational pharmacology
- Adaptive clinical trial design

C9orf72

WVE-004

Variant-selective silencing candidate in ALS and FTD

SNP3

WVE-003

Allele-selective silencing candidate in HD

Exon 53

WVE-N531

Exon skipping candidate in DMD

WAVE LIFE SCIENCES

HD: Huntington's disease ALS: amyotrophic lateral sclerosis FTD: frontotemporal dementia DMD: Duchenne muscular dystrophy

WAVE™
LIFE SCIENCES

WVE-004

Amyotrophic Lateral Sclerosis (ALS)

Frontotemporal Dementia (FTD)

C9orf72 repeat expansions: One of the most common genetic causes of ALS and FTD

Hexanucleotide (G_4C_2)- repeat expansions in C9orf72 gene are common autosomal dominate cause for ALS and FTD

Different manifestations across a clinical spectrum

Amyotrophic Lateral Sclerosis (ALS)

- Fatal neurodegenerative disease
- Progressive degeneration of motor neurons in brain and spinal cord
- C9-specific ALS: ~2,000 patients in US

Frontotemporal Dementia (FTD)

- Progressive neuronal degeneration in frontal/temporal cortices
- Personality and behavioral changes, gradual impairment of language skills
- C9-specific FTD: ~10,000 patients in US

WVE-004 is the first therapy in clinical development for both C9-ALS and C9-FTD

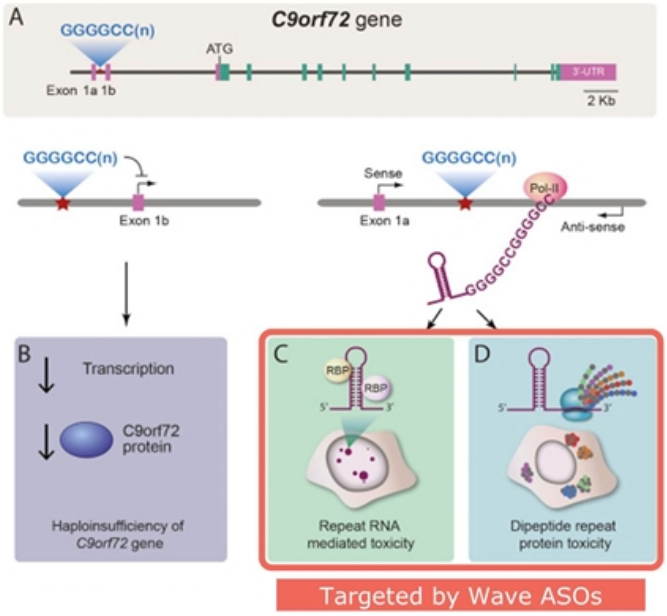
WAVE LIFE SCIENCES

Sources: Balendra et al, EMBO Mol Med, 2017; Brown et al, NEJM, 2017, DeJesus-Hernandez et al, Neuron, 2011. Renton et al, Neuron, 2011. Zhu et al, Nature Neuroscience, May 2020, Stevens et al, Neurology 1998

C9orf72 repeat expansions: Mechanisms of cellular toxicity

- C9-ALS and C9-FTD may be caused by multiple factors:
  - Insufficient levels of C9orf72 protein
  - Accumulation of repeat-containing RNA transcripts
  - Accumulation of aberrantly translated DPR proteins
- Recent evidence suggests lowering C9orf72 protein exacerbates DPR-dependent toxicity

Variant-selective targeting could address multiple potential drivers of toxicity

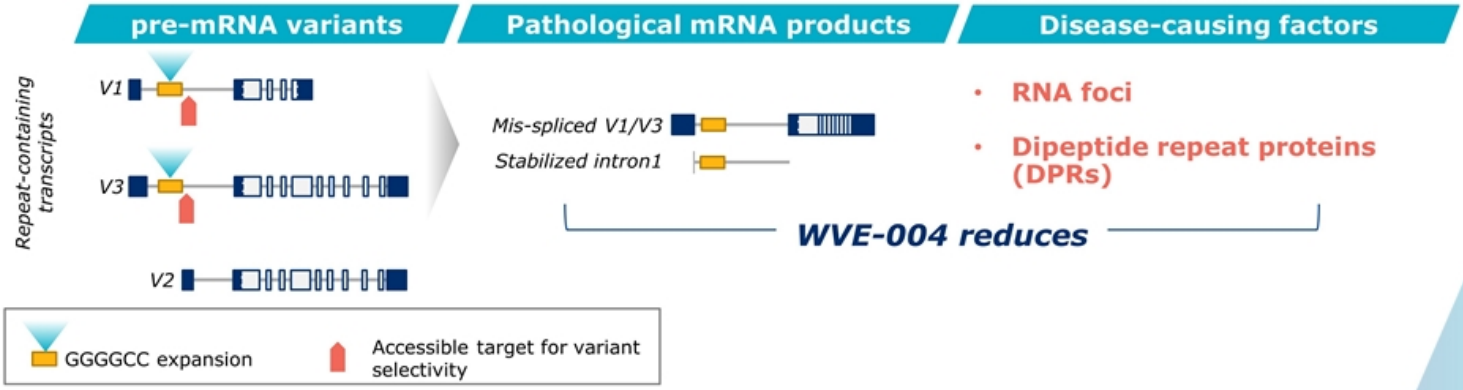


WAVE LIFE SCIENCES

Sources: Gitler et al, Brain Research, September 2016. Zhu et al, Nature Neuroscience, May 2020

C9orf72 targeting strategy spares C9orf72 protein

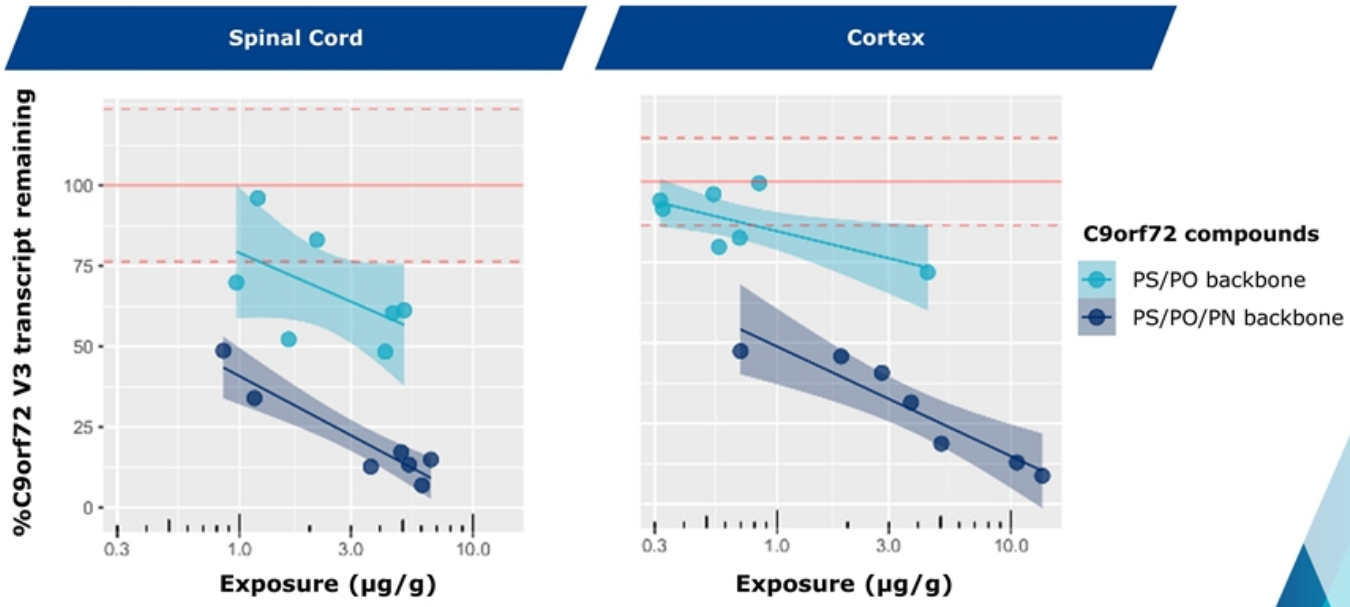
- Normal C9orf72 allele produces three mRNA transcripts (~80% are V2, ~20% are V1 and V3)
- **Pathological allele** with expanded repeat leads to **healthy V2** and **pathological V1 and V3** transcript by-products



WVE-004 targets only V1 and V3 transcripts, sparing V2 transcripts and healthy C9orf72 protein

WAVE LIFE SCIENCES

PN backbone chemistry modifications: Improved potency among C9orf72-targeting oligonucleotides *in vivo*

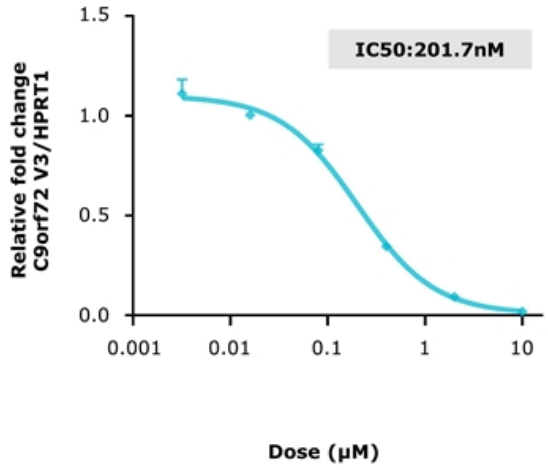


WAVE LIFE SCIENCES

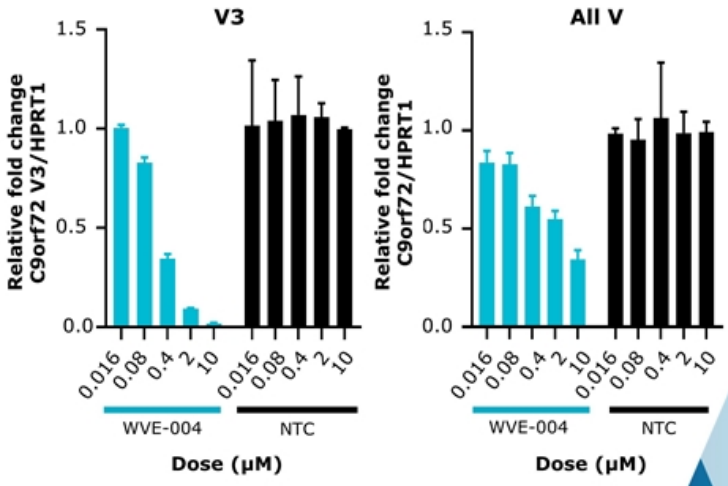
Mice received 2 x 50 ug ICV doses on days 0 & 7; mRNA from spinal cord and cortex quantified by PCR (Taqman assay) 8 weeks later. Oligonucleotide concentrations quantified by hybridization ELISA. Graphs show robust best fit lines with 95% confidence intervals (shading) for PK-PD analysis.

WVE-004: Potent and selective knockdown of repeat-containing transcripts *in vitro*

In vitro activity in C9 patient-derived neurons



In vitro selectivity in C9 patient-derived neurons

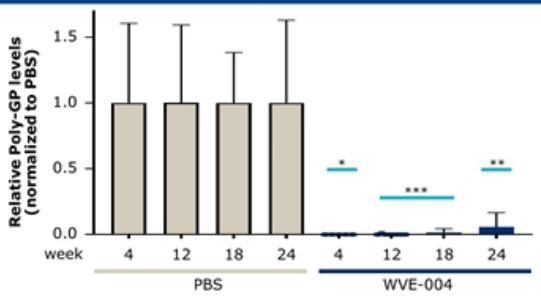


WAVE LIFE SCIENCES

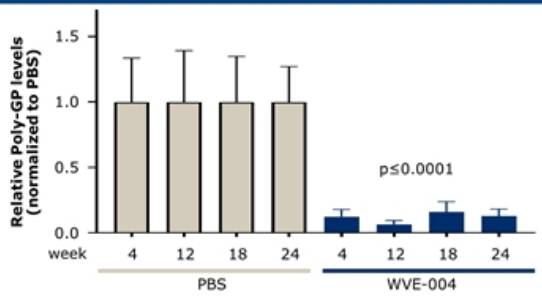
C9 patient-derived motor neurons were treated with C9orf72 candidate and NTC under gymnotic conditions up to 10uM. Taqman qPCR assays were used to evaluating V3 and all V transcripts. NTC- non-targeting control.

WVE-004 demonstrates durable reduction of DPRs in vivo after 6 months in spinal cord and cortex

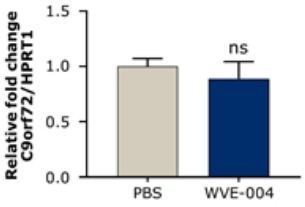
Spinal cord

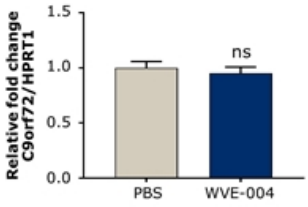


Cortex



Healthy C9orf72 protein relatively unchanged ~6 months after WVE-004 administration





WAVE LIFE SCIENCES

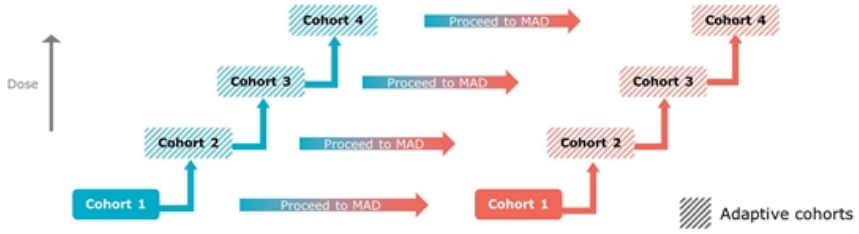
Full results presented at the 31st International Symposium on ALS/ MND (December 2020)
Top: 2 x 50 ug (day 0, day 7) dosed ICV; DPRs measured by Poly-GP MSD assay. *: p≤ 0.05 **: P ≤ 0.01, ***: P ≤ 0.001. ICV: intracerebroventricular; DPR: Dipeptide repeat protein; Bottom: C9 BAC transgenic mice administered PBS or 50 ug WVE-004, ICV, (day 0, day 7). ns: not significant; PBS: phosphate-buffered saline

FOCUS-C9: Adaptive trial designed to enable rapid assessment of target engagement

Phase 1b/2a global, multicenter, randomized, double-blind, placebo-controlled trial

FOCUS C9

Targeting 50 patients with C9-ALS, C9-FTD or mixed phenotype



Single-ascending dose (SAD)

Day	1-3	15	29	57	85
Dose	▼				
Biomarker Samples	●	●	●	●	●
Clinical Evaluations	●		●	●	●

Multi-ascending dose (MAD)

Week	1	4	8	12	16	20	24
	▼	▼	▼	▼			
	●	●	●	●	●	●	●
	●	●	●	●	●	●	●

Primary objectives

- Safety and tolerability

Secondary objectives

- Plasma and CSF PK profile
- PolyGP in CSF

Exploratory objectives

Biomarkers:

- p75NTR^{ECD} in urine
- NfL in CSF

Clinical endpoints:

- ALSFRS-R
- CDR-FTDLD
- FVC
- HHD

Dose escalation and MAD dosing frequency guided by independent committee

WAVE LIFE SCIENCES

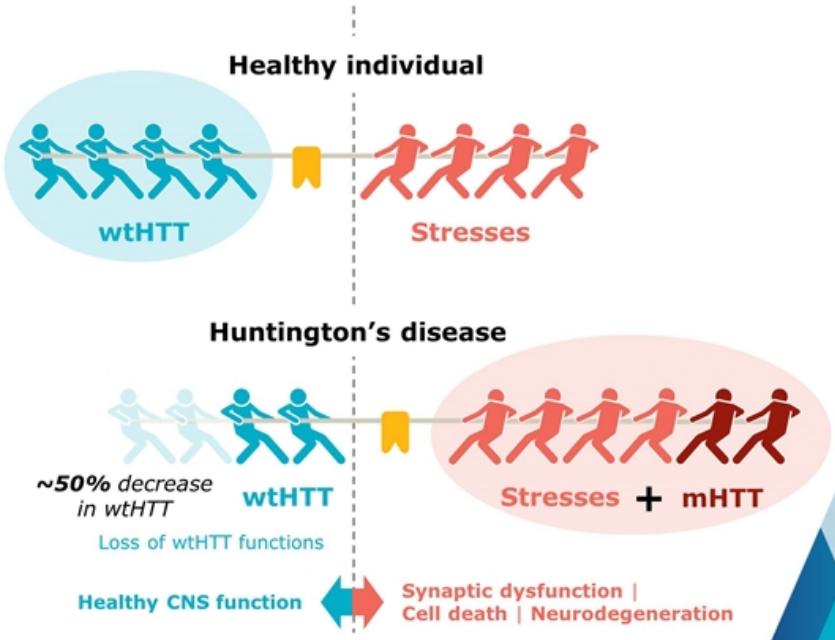
WAVE™
LIFE SCIENCES

WVE-003

Huntington's Disease

mHTT toxic effects lead to neurodegeneration, loss of wtHTT functions may also contribute to HD

- Wild-type HTT is critical for normal neuronal function
- Expanded CAG triplet repeat in HTT gene results in production of mutant huntingtin protein
- Huntington's disease affects entire brain
- Monogenic autosomal dominant genetic disease; fully penetrant
- Characterized by cognitive decline, psychiatric illness, and chorea; fatal disease



WAVE LIFE SCIENCES

HD: Wild-type HTT is a critical protein for important functions in the central nervous system

NEURON

Promotes neuronal survival by protecting against stress (e.g., excitotoxicity, oxidative stress, toxic mHTT aggregates)[1-8]

SYNAPSE

Plays an essential role in the transport of synaptic proteins—including neurotransmitters and receptors—to their correct location at synapses[9-12]

BRAIN CIRCUITS

Supplies BDNF to the striatum to ensure neuronal survival[13-16]

Regulates synaptic plasticity, which underlies learning and memory[17-22]

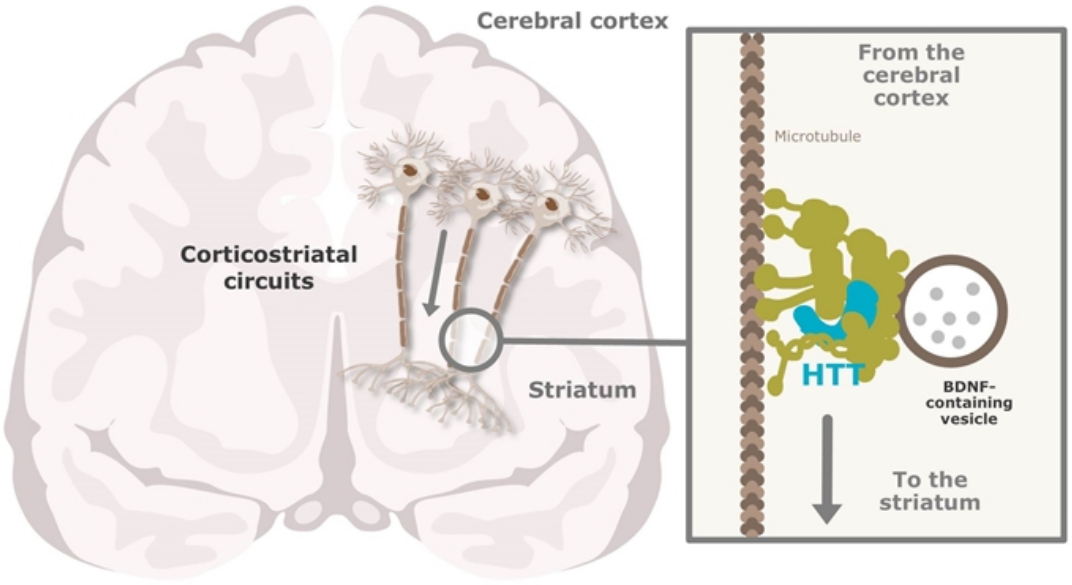
CSF CIRCULATION

Plays a critical role in formation and function of cilia—sensory organelles that control the flow of CSF—which are needed to clear catabolites and maintain homeostasis[23]

WAVE LIFE SCIENCES

BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; mHTT, mutant huntingtin protein. Sources: 1. Leavitt 2006 2. Cattaneo 2005 3. Kumar 2016 4. Franco-Iborra 2020 5. Hamilton 2015 6. Ochaba 2014 7. Wong 2014 8. Rui 2015 9. Caviston 2007 10. Twelvetrees 2010 11. Strehlow 2007 12. Milnerwood 2010 13. Smith-Dijak 2019 14. Tousley 2019 15. Zhang 2018 16. McAdam 2020 17. Altar 1997 18. Zuccato 2001 19. Gauthier 2004 20. Ferrer 2000 21. Baquet 2004 22. Liu 2011 23. Karam 2015

HTT provides BDNF, a growth factor critical for survival of striatal neurons



Striatal neurons do not produce BDNF, but they need it to survive[1]

HTT promotes the production of BDNF and transports BDNF from the **cortex** to the striatum[2,3]

In HD, decreased levels of BDNF contribute to degeneration of corticostriatal circuits[2,4,5]

Reduction of wtHTT may decrease the availability of BDNF and accelerate corticostriatal degeneration[6]

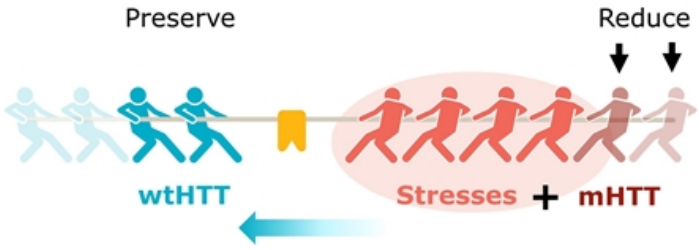
BDNF, brain-derived neurotrophic factor; HD, Huntington's disease; HTT, huntingtin protein.

1. Altar CA, Cai N, Bliven T, et al. *Nature*. 1997;389(6653):856-860. 2. Zuccato C, Ciammola A, Rigamonti D, et al. *Science*. 2001;293(5529):493-498. 3. Gauthier LR, Charrin BC, Borrell-Pagès M, et al. *Cell*. 2004;118(1):127-138. 4. Ferrer I, Goutan E, Marín C, et al. *Brain Res*. 2000;866(1-2):257-261. 5. Baquet ZC, Gorski JA, Jones KR. *J Neurosci*. 2004;24(17):4250-4258. 6. Cattaneo E, et al. *Nat Rev Neurosci*. 2005;6(12):919-930.

Allele-selective approach to treating HD

Wave has only allele-selective clinical program in Huntington's disease

- ✓ Target mutant mRNA HTT transcript to reduce mutant HTT protein
- ✓ Preserve wild-type HTT protein reservoir in brain



Only an allele-selective approach is designed to address <u>both</u> toxic gain of function and toxic loss of function drivers of HD

WAVE LIFE SCIENCES

Allele-selective approach to treating HD

~40% of HD Patients Carry SNP3

Allele-selective Treatments Have Potential to Benefit Many of Those At-risk of HD

Personalized approach to wtHTT sparing opens possibility of early treatment

WAVE LIFE SCIENCES

[1] Claassen et al. Neurol Genet Jun 2020; Carroll et al. Mol Ther. 2011 Dec; HDSA.org

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

nature

Article

Injured adult neurons regress to an embryonic transcriptional growth state

https://doi.org/10.1038/s41586-020-2200-5
Received: 12 April 2019
Accepted: 13 February 2020
Published online: 15 April 2020
Check for updates

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

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

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

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

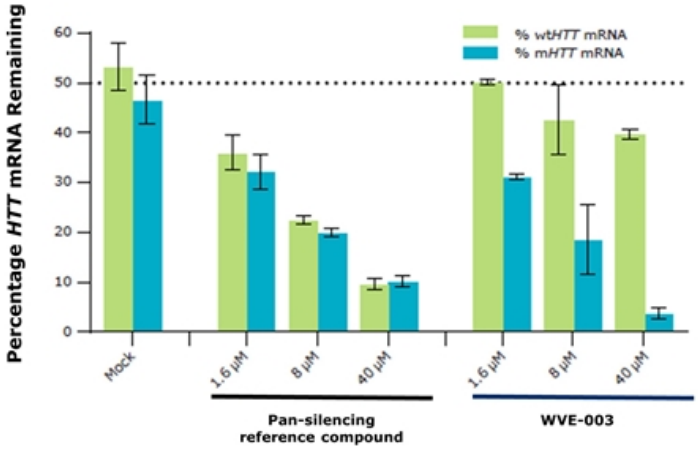
WAVE LIFE SCIENCES

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

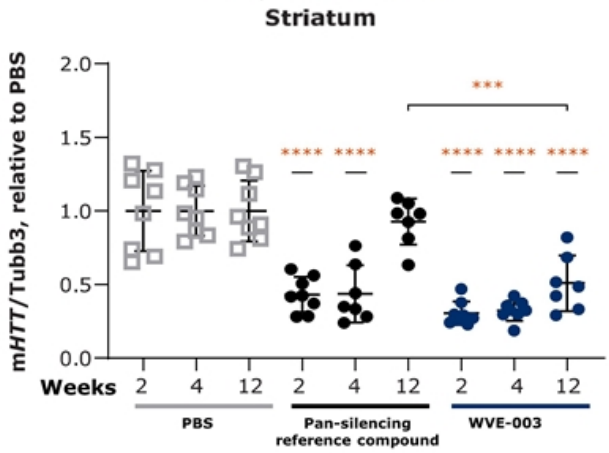
WVE-003 (SNP3) demonstrates selective, potent, and durable reduction of mHTT in preclinical models

Incorporates PN backbone chemistry modifications

Selectively reduces mHTT mRNA in HD iPSC neurons in vitro



Durable striatal mHTT knockdown for 12 weeks in BACHD mouse model



WAVE LIFE SCIENCES

Results from ND50036 iPSC-derived medium spiny neurons. Total *HTT* knockdown quantified by qPCR and normalized to HPRT1
Oligonucleotide or PBS [100 µg ICV injections through a cannula on days 1, 3, and 5] delivered to BACHD transgenic. Mean ± SD (n=8, **P*<0.0332, ****P*<0.0002, *****P*<0.0001 versus PBS unless otherwise noted).
HPRT1, hypoxanthine-guanine phosphoribosyl transferase; iPSC, induced pluripotent stem cell; ICV, intracerebroventricular; PBS, phosphate-buffered saline

WVE-003: *In vivo* studies support distribution to cortex and striatum in BACHD and NHPs

BACHD model

Achieved maximum mHTT knockdown of 70-75% in **cortex** and **striatum** with ~50% knockdown persisting for at least 3 months with WVE-003

NHP

Achieved sufficient concentrations of WVE-003 in **cortex** and **striatum** for target engagement

Human

Anticipated mHTT knockdown in **cortex** and **striatum** based on PK-PD modeling

Clinical starting dose of WVE-003 informed by PK-PD modeling

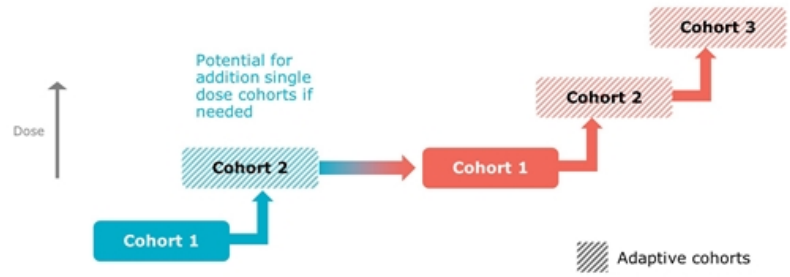
WAVE LIFE SCIENCES

PK: pharmacokinetic PD: pharmacodynamic IC_{50}: the concentration of observed half of the maximal effect mHTT: mutant huntingtin protein

SELECT-HD: Adaptive trial designed to enable faster optimization of dose and frequency

Phase 1b/2a global, multicenter, randomized, double-blind, placebo-controlled trial

Targeting 36 patients with early manifest HD diagnosis with SNP3 variant



Primary objectives

- Safety and tolerability

Secondary objectives

- Plasma PK profile
- CSF exposure

Exploratory objectives

Biomarkers:

- mHTT
- wtHTT
- NfL

Clinical endpoints:

- UHDRS

Single-ascending dose (SAD)

Day	1-3	15	29	57	85
Dose	▼				
Biomarker Samples	●	●	●	●	●
Clinical Evaluations	●				●

Multi-ascending dose (MAD)

Week	1	2	4	8	12	16	20	24
	▼	▼	▼	▼	▼			
	●	●	●	●	●	●	●	●
	●				●		●	

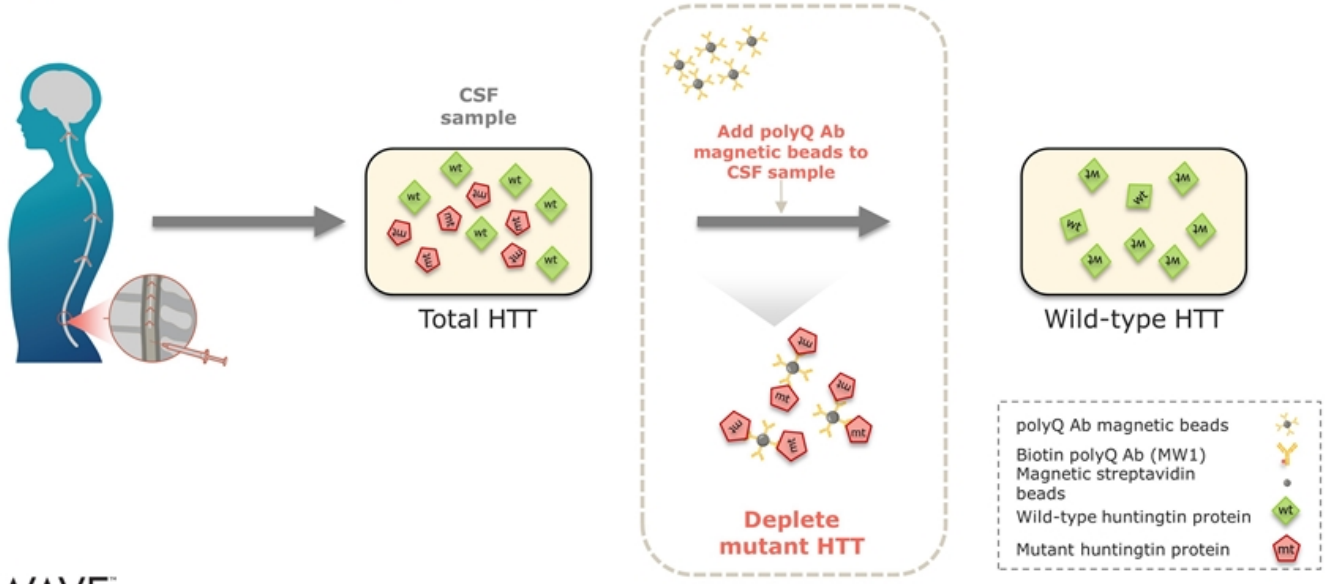
Dose escalation and MAD dosing frequency guided by independent committee

WAVE LIFE SCIENCES

mHTT: mutant huntingtin; wtHTT: wild-type huntingtin; NfL: neurofilament light

Assessment of wild-type protein in CSF

Depletion of mutant HTT key to ability to measure wild-type HTT protein



WAVE LIFE SCIENCES

Ab: antibody CSF: cerebrospinal fluid HTT: huntingtin protein MW1: Wild et al. JCI 2015

WAVE™
LIFE SCIENCES

WVE-N531

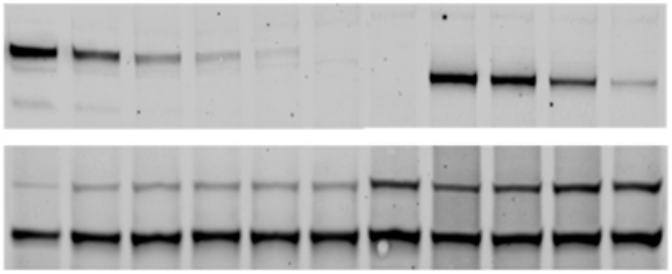
Duchenne muscular dystrophy

WVE-N531 *in vitro* dose-dependent dystrophin restoration

Dystrophin protein restoration of up to 71%

Western Blot normalized to primary healthy human myoblast lysate

Standard Curve (% WT lysate in D45-52 lysate)						D45-52 Cells					
						Mock	WVE-N531				
						0	10	3.3	1.1	0.3	Conc [uM]
100%	50%	25%	12%	6%	0%	0%	71%	65%	37%	9.5%	% Dystrophin



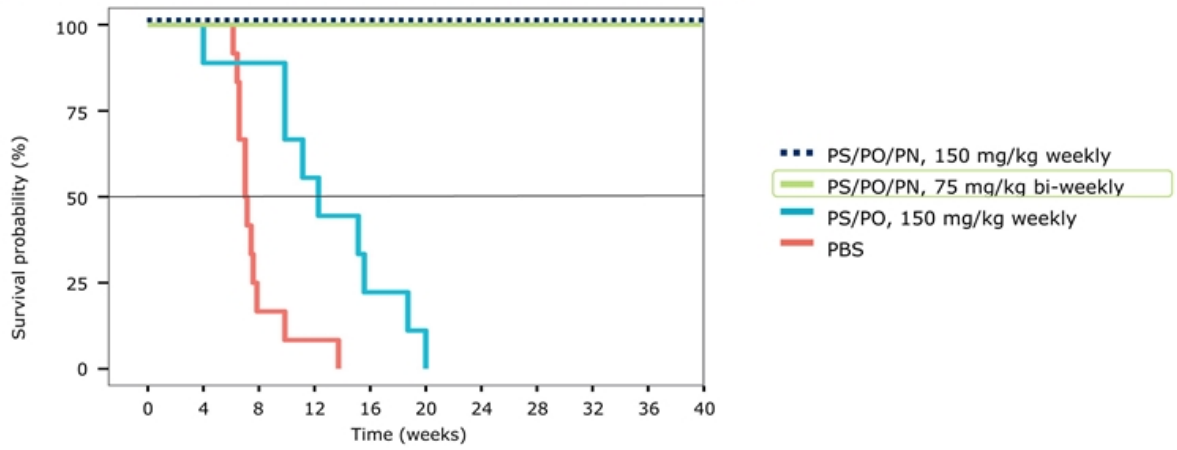
- WVE-N531 contains novel PN backbone chemistry modifications
- Free uptake for 6 days in differentiation media with no transfection agent and no peptide conjugated to the oligonucleotide
- Demonstrated a dose-dependent increase in dystrophin restoration in DMD patient-derived myoblasts

WAVE LIFE SCIENCES

Experimental conditions: Δ45-52 (D45-52) patient myoblasts were treated with oligonucleotide for 6d under free-uptake conditions in differentiation media. Protein harvested in RIPA buffer and dystrophin restoration analyzed by Western Blot. Signal normalized to vinculin loading control and to primary healthy human myotube lysate (pooled from four donors) forming a standard curve in Δ45-52 cell lysate.

PN chemistry led to overall survival benefit in dKO model

PN-containing molecules led to 100% dKO survival at time of study termination



Note: Untreated, age-matched mdx mice had 100% survival at study termination [not shown]

WAVE LIFE SCIENCES

dKO; double knockout mice lack dystrophin and utrophin protein. mdx mice lack dystrophin. Left: Mice with severe disease were euthanized. dKO: PS/PO/PN 150 mg/kg n= 8 (p=0.0018); PS/PO/PN 75 mg/kg n=9 (p=0.00005); PS/PO n=9 (p=0.0024), PBS n=12 Stats: Chi square analysis with pairwise comparisons to PBS using log-rank test

Clinical trial of WVE-N531 to initiate in 2021

- Unmet need in DMD remains high
- CTA submitted in March 2021 to initiate clinical development
- Clinical trial powered to evaluate change in dystrophin production, and will assess drug concentration in muscle, and initial safety
  - Open-label study; targeting every-other-week administration in up to 15 boys with DMD
- Potential to apply PN chemistry to other exons if successful

Dosing in clinical trial expected to initiate in 2021

WAVE LIFE SCIENCES

WAVE™
LIFE SCIENCES

Wave's discovery and drug development platform

Rational drug design: Evolution of PRISM platform

Addressing the reality of stereochemistry

Choosing to control for stereochemistry enables Wave to apply principles of rational drug design to oligonucleotides

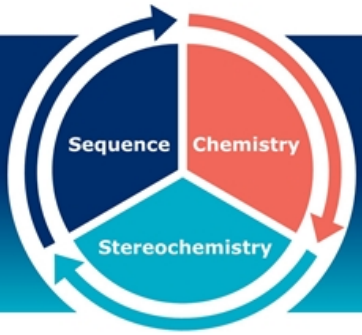
WAVE LIFE SCIENCES

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 machine learning-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

Multiple modalities
Silencing | Splicing | ADAR editing

WAVE LIFE SCIENCES

PRISM platform enables rational drug design

Sequence

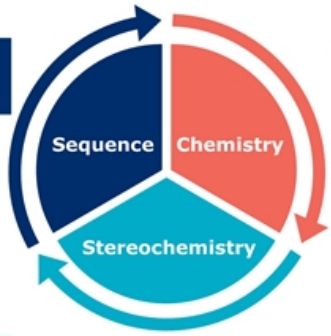
B: bases

A, T, C, mC, G, U,
other modified bases

Stereochemistry

Chiral control of
any stereocenter

5′ modifications,
backbone modifications



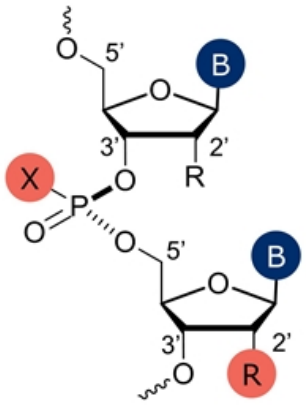
Chemistry

R: 2′ modifications

OMe, MOE, F,
other modifications

X: backbone chemistry

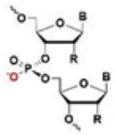
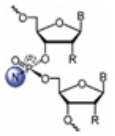
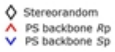
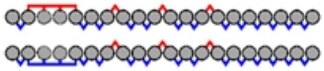
Phosphodiester (PO),
phosphorothioate (PS),
Phosphoramidate diester
(PN)

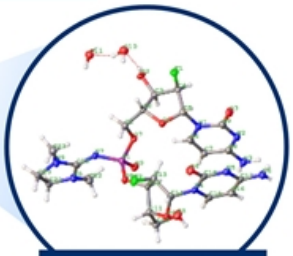


WAVE LIFE SCIENCES

Expanding repertoire of backbone modifications with novel PN backbone chemistry

Backbone linkages

	PO	PS	PN
Backbone modification (X)	Phosphodiester 	Phosphorothioate 	Phosphoramidate diester 
Stereochemistry	Not chiral	Chiral 	Chiral 
Charge	Negative	Negative	Neutral
Depiction			
PRISM backbone modifications	PO/PS		
	PO/PS/PN		

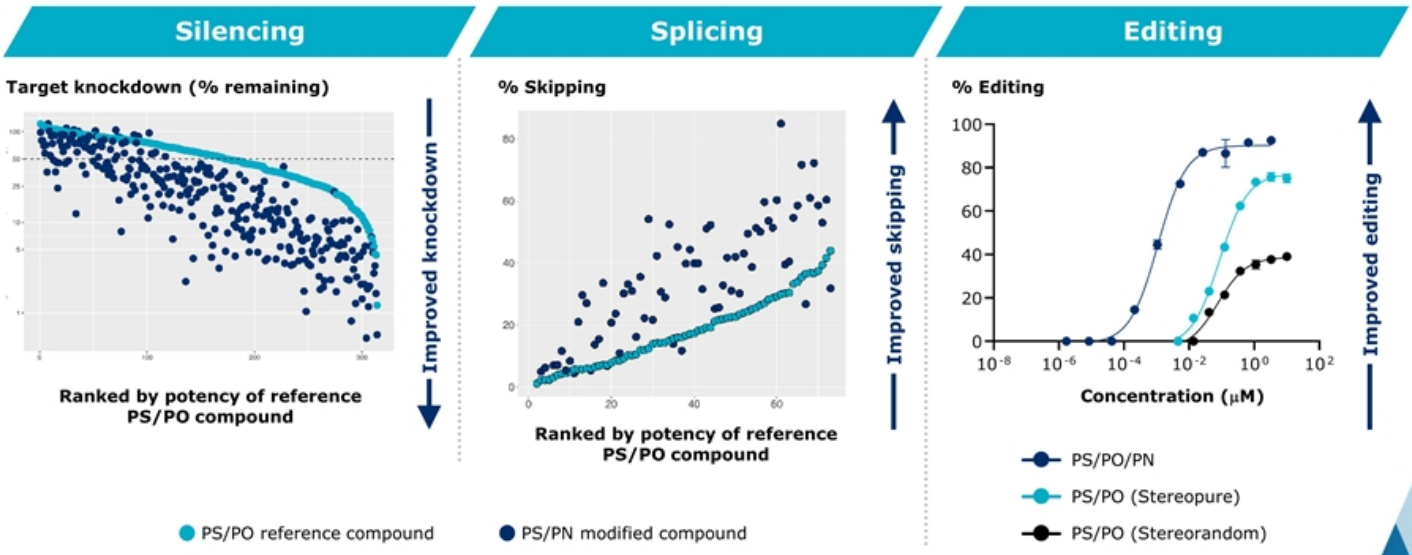


Phosphoryl guanidine x-ray structure

WAVE LIFE SCIENCES

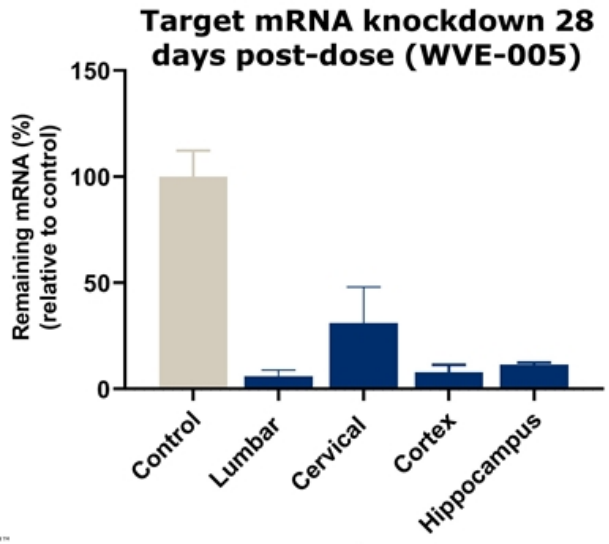
Molecule structure illustrative of backbone modification patterns

PN chemistry increases potency in silencing, splicing, and editing preclinical studies



Lead program in Takeda collaboration reinforces potential of PN chemistry in the CNS

Substantial and widespread target mRNA reduction following single intrathecal dose in NHPs

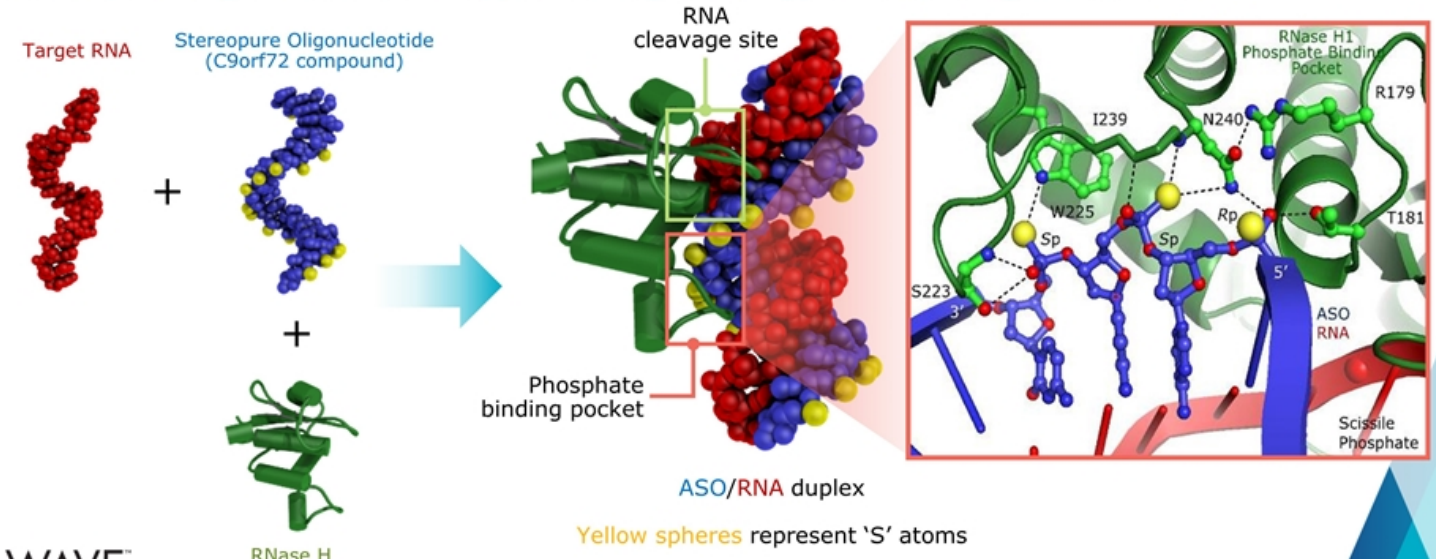


- Single IT dose of 12 mg (n=3)
- Therapeutic candidate widely distributed across brain and spinal cord
- ~90% mRNA knockdown one-month following single dose

NHPs: Non-human primates; IT: intrathecal
NHPs were administered 12 mg on day 1 via IT bolus injection; tissue samples were collected from 3 NHPs at 28 days post-dose.
WVE-005 is lead program in Takeda collaboration for an undisclosed CNS target

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

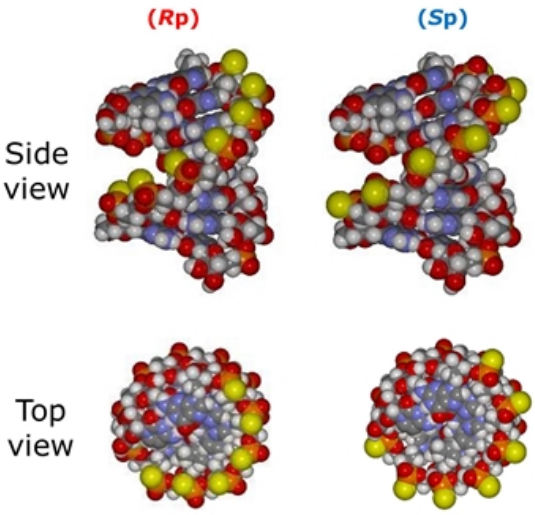


ASO/RNA duplex

Yellow spheres represent 'S' atoms

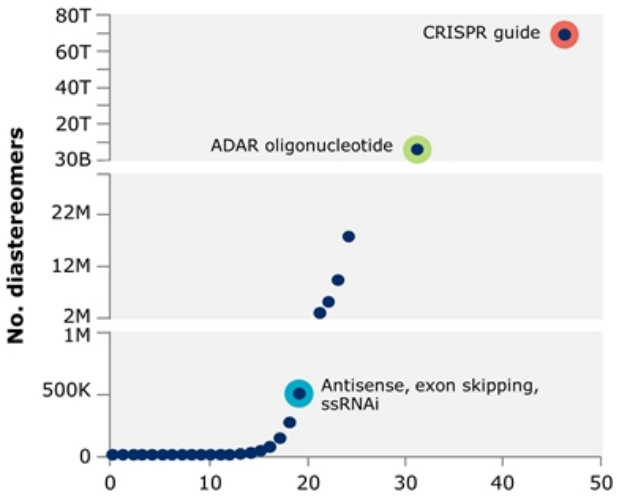
Importance of controlling stereochemistry

Stereochemical diversity



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

Exponential diversity arises from uncontrolled stereochemistry



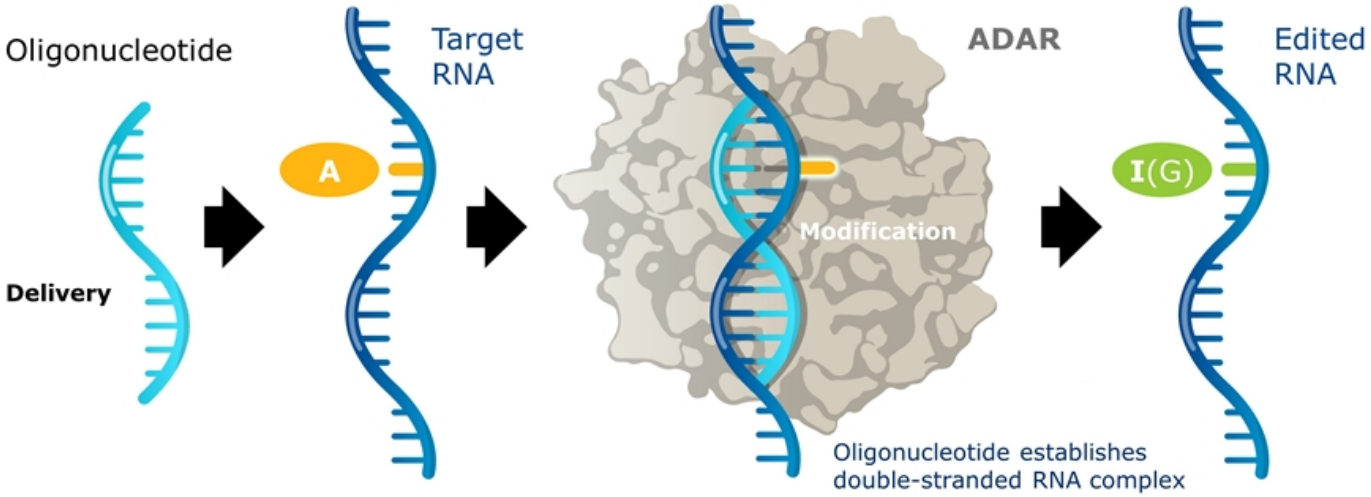
Number of PS linkages in oligonucleotide backbone

WAVE™
LIFE SCIENCES

ADAR editing

Platform capability and Alpha-1 antitrypsin deficiency

PRISM platform has unlocked ADAR editing

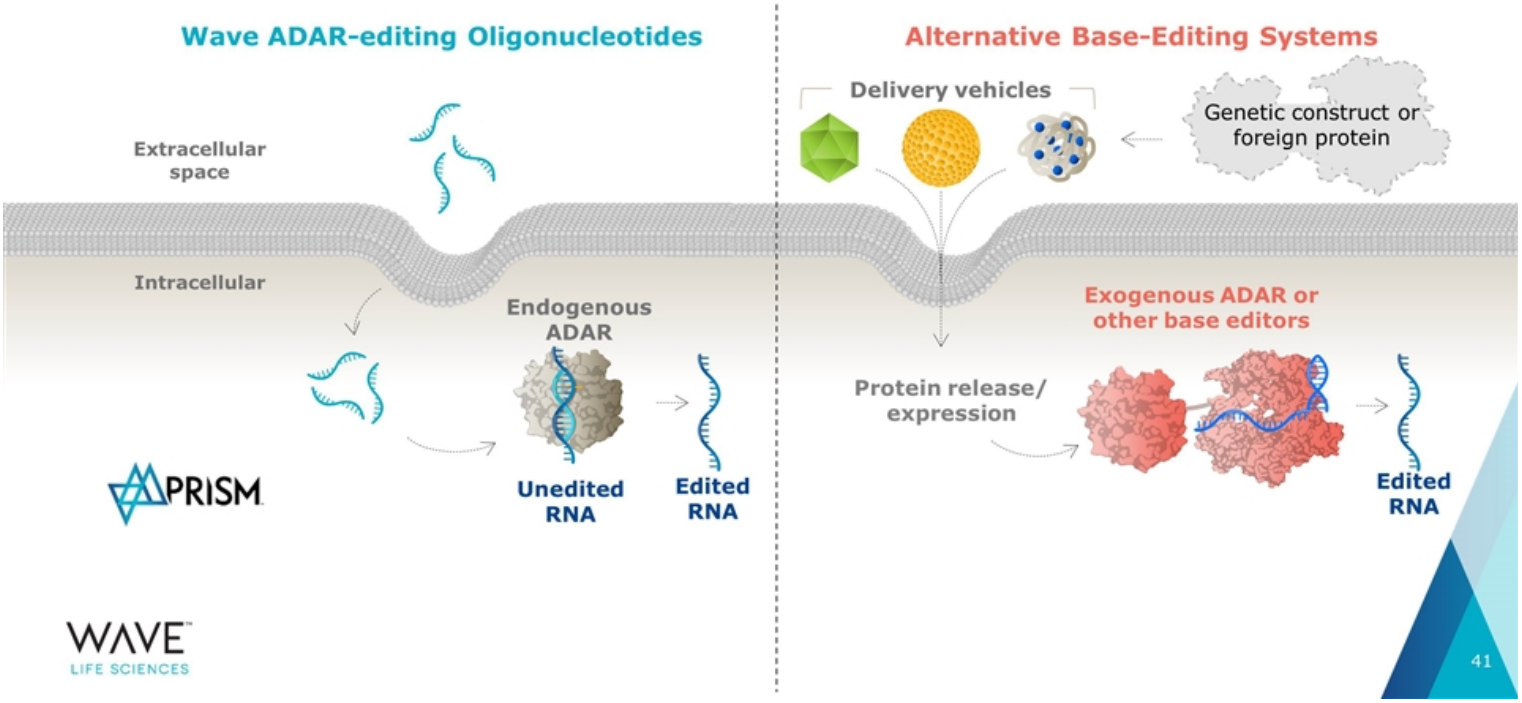


- **A**-to-**I** editing is one of most common post-transcriptional modifications
- ADAR is ubiquitously expressed across tissues, including liver and CNS

WAVE LIFE SCIENCES

A: adenosine; I: inosine; G: guanosine; Nishikura, K. A-to-I editing of coding and non-coding RNAs by ADARs. Nat. Rev. Mol. Cell Biol. 2016; Picardi, E. *et al.* Profiling RNA editing in human tissues: towards the inosinome Atlas. *Scientific reports* **5**, 14941, doi:10.1038/srep14941 (2015).

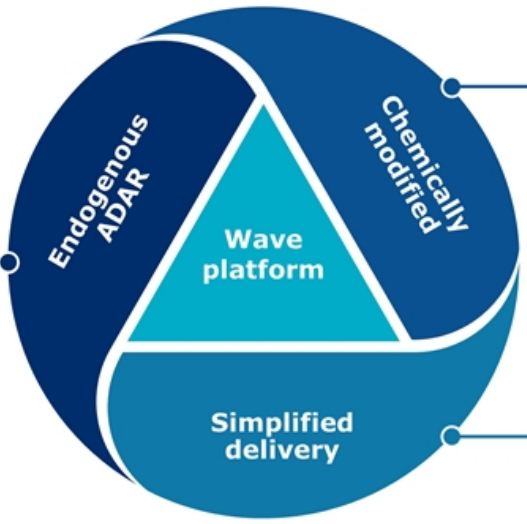
PRISM enables practical approach to RNA editing without need for viruses or exogenous protein



WAVE LIFE SCIENCES

Advantages of Wave ADAR editing platform

- Avoids permanent off-target DNA edits
- No immunogenicity from exogenous proteins
- Reduced off-target effects



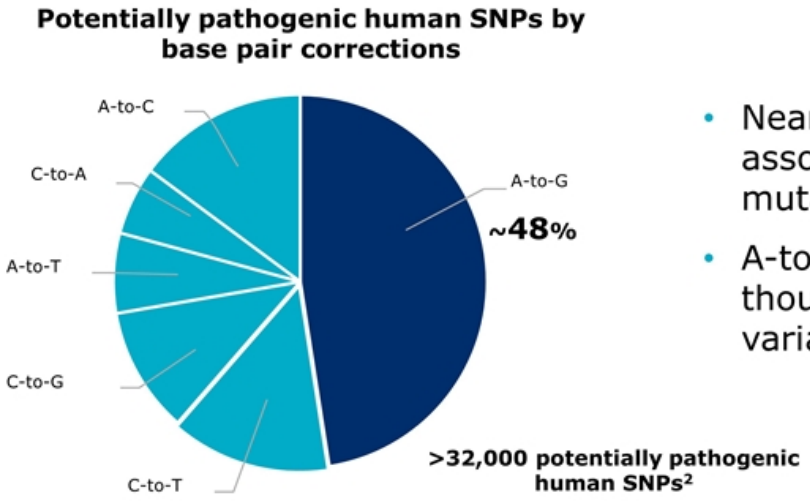
- Fully chemically modified to increase stability *in vivo*
- Chirally-controlled backbone to maximize *in vitro* activity
- PN backbone chemistry modification improves editing efficiency

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

WAVE LIFE SCIENCES

Sources: Chen Biochemistry 2019

ADAR amenable diseases represent a sizeable opportunity



- Nearly half of known human SNPs associated with disease are G-to-A mutations
- A-to-I(G) editing could target tens of thousands of potential disease variants[1]

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

RNA editing opens many new therapeutic applications

Restore protein function

- Fix nonsense and missense mutations that cannot be splice-corrected
- Remove stop mutations
- Prevent protein misfolding and aggregation

Examples:

Recessive or dominant genetically defined diseases

Modify protein function

- Alter protein processing (e.g. protease cleavage sites)
- Protein-protein interactions domains
- Modulate signaling pathways

Examples:

Ion channel permeability

Protein upregulation

- miRNA target site modification
- Modifying upstream ORFs
- Modification of ubiquitination sites

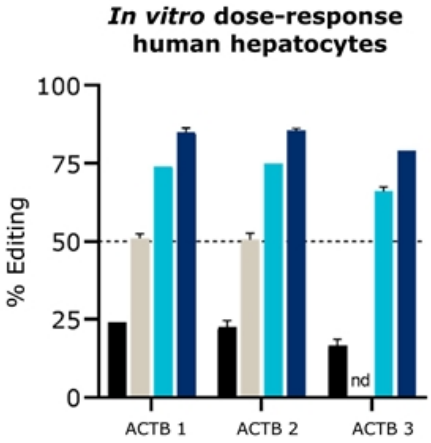
Examples:

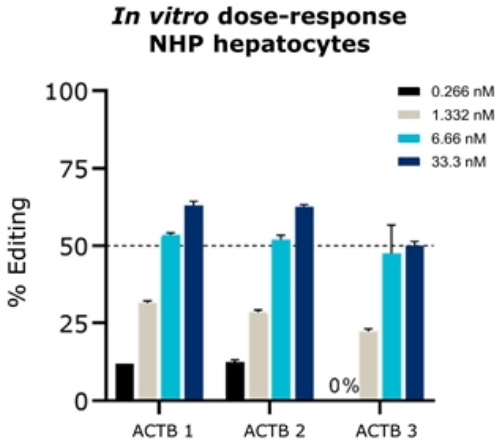
Haploinsufficient diseases

WAVE LIFE SCIENCES

Significant ADAR editing demonstrated *in vitro* in NHP and primary human hepatocytes

ACTB GalNAc-conjugated oligonucleotides with stereopure PN backbone chemistry modifications





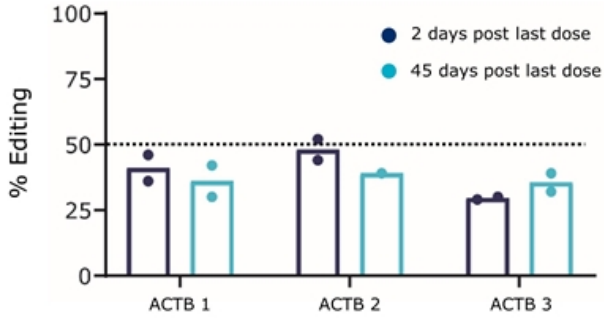
WAVE LIFE SCIENCES

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.

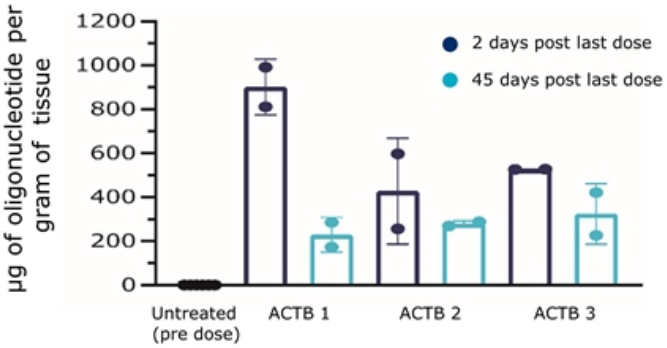
Efficient ADAR editing translated *in vivo* in non-human primate study

- Up to 50% editing efficiency observed at Day 7, 2 days post last dose
- Substantial and durable editing out to at least Day 50, 45 days post last dose

In vivo editing in NHP following subcutaneous administration



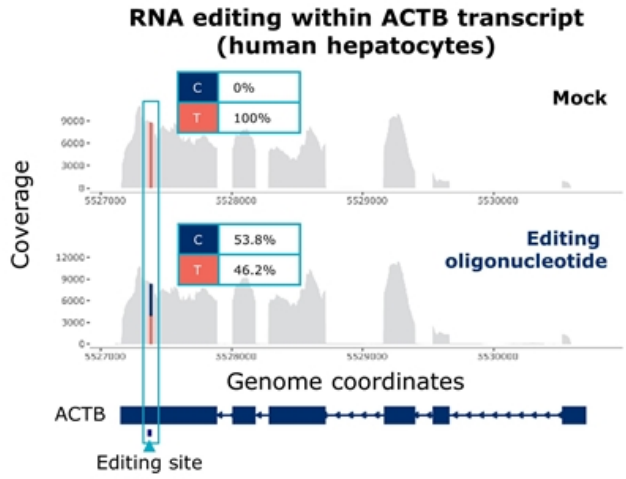
Oligonucleotide quantification in NHP following subcutaneous administration



WAVE LIFE SCIENCES

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

Wave ADAR editing oligonucleotides are highly specific



WAVE LIFE SCIENCES

Human hepatocytes were dosed with 1um oligonucleotide, 48 hours later RNA was collected and sent for RNA sequencing. RNAseq conducted using strand-specific libraries to quantify on-target ACTB editing and off-target editing in primary human hepatocytes; plotted circles represent sites with LOD>3

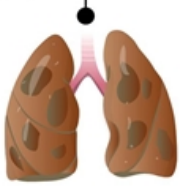
ADAR editing approach may simultaneously address lung and liver manifestation of AATD

Alpha-1 antitrypsin deficiency (AATD)

Most common cause is mutation in *SERPINA1* Z allele

Z-AAT misfolded protein prone to aggregation

Dual Pathologies in AATD



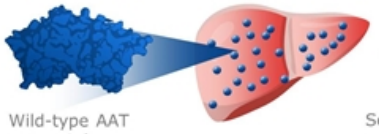
- **~200K people in US and EU** with homozygous ZZ genotype, most common form of severe AATD
- Approved therapies modestly increase circulating levels of wild-type AAT in those with lung pathology; no therapies address liver pathology

Inability to secrete polymerized Z-AAT, leading to **liver damage/cirrhosis**

Open to unchecked proteases, leading to inflammation and **lung damage**

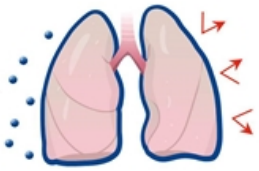
Wave's ADAR editing approach

GalNAc oligonucleotide to correct *SERPINA1* Z allele mRNA



Wild-type AAT protein

Secretion into bloodstream



Lungs protected from proteases

✓ **Restores** wild-type AAT physiological regulation **in liver**, reducing Z-AAT protein aggregation

✓ Increases circulating, **lung-bound** wild-type AAT

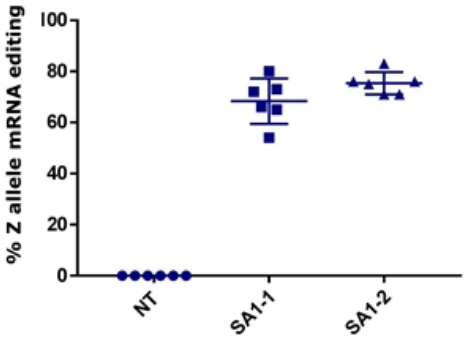
WAVE LIFE SCIENCES

AAT: Alpha-1 antitrypsin; Sources: Strnad 2020; Blanco 2017

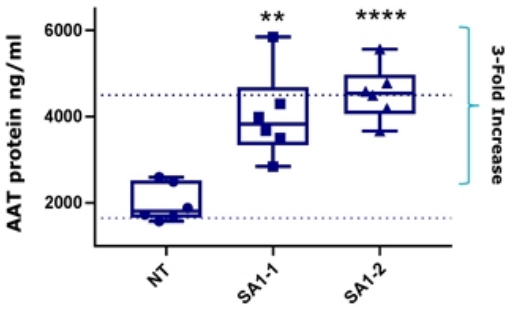
SERPINA1 Z allele mRNA editing increases edited AAT protein concentration *in vitro*

In primary hepatocyte *SERPINA1* Z cell model, editing the Z allele mRNA back to wild-type prevents protein misfolding and increases secretion of edited AAT protein from hepatocytes

SERPINA1 Z allele mRNA editing



AAT protein concentration in media



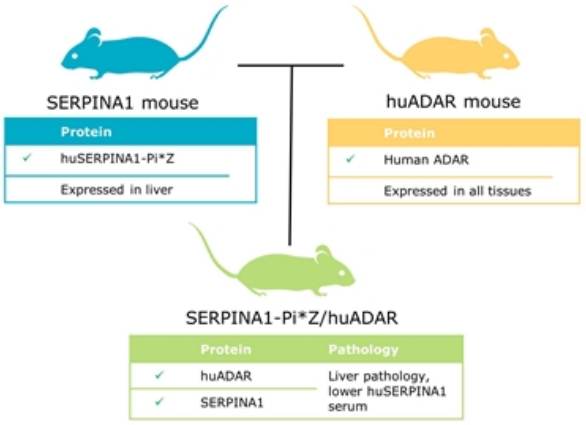
Edited AAT protein analysis

- Wild-type AAT protein confirmed by mass spectrometry
- Function of secreted, edited AAT protein confirmed by neutrophil elastase inhibition assay

Model validation and *in vivo* data expected 1H 2021

AAT (alpha-1 antitrypson); Mouse primary hepatocytes that express SERPINA1 Z allele mRNA were transfected with 25 nanomolar (nM) of SERPINA1 (SA1-1 and SA1-2) targeting antisense oligonucleotides (ASOs) and a control non-targeting (NT) ASO. Media and RNA was collected at 5 days post transfection. AAT protein in media was quantified by Elisa Assay, RNA editing was quantified by RT/PCR/Sanger sequencing.

Proprietary humanized mouse model developed to support ADAR platform



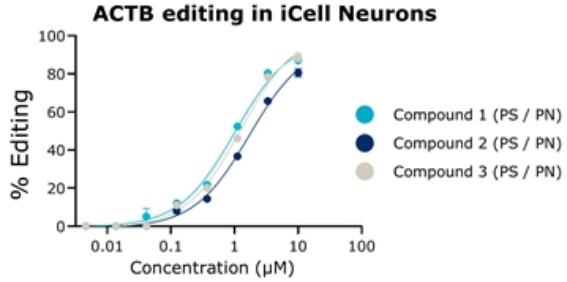
- Expression of huADAR in mouse is comparable to expression in human cells
- Expression of huADAR restores editing of endogenous targets in primary mouse cell types to levels seen in human primary cell types
- huADAR mouse model can be crossed with disease specific mouse models to provide model systems for use across Wave's ADAR editing programs

Model validation and *in vivo* data expected 1H 2021

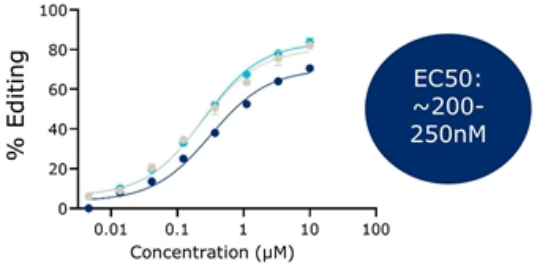
WAVE LIFE SCIENCES

Multiple opportunities for ADAR editing in neurology

ACTB editing in iCell Neurons



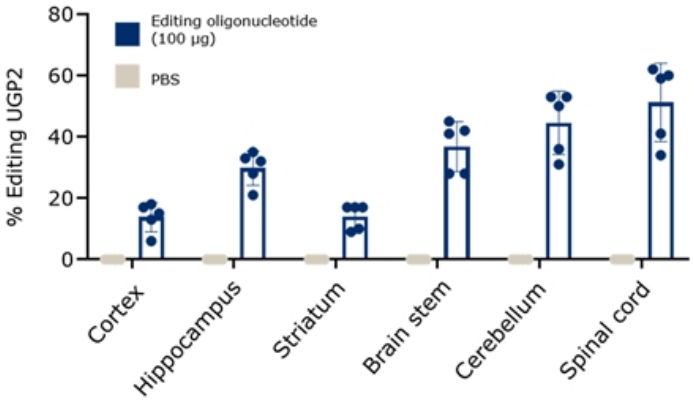
ACTB editing in human iCell Astrocytes



EC50: ~200-250nM

Gymnotic uptake; Total RNA was harvested, reverse transcribed to generate cDNA, and the editing target site was amplified by PCR and quantified by Sanger sequencing

***In vivo* CNS editing in proprietary hADAR transgenic mouse (1 week)**



hADAR: human ADAR; UGP2: Glucose Pyrophosphorylase 2; 5 mice in each group were injected with PBS or a single 100uG dose on day 0. Animals were necropsied on day 7. RNA was harvested and editing measured by Sanger sequencing.

WAVE™
LIFE SCIENCES

Ophthalmology

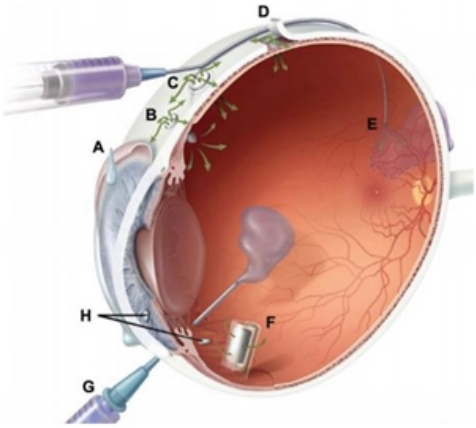
Stereopure oligonucleotides for inherited retinal diseases (IRDs)

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

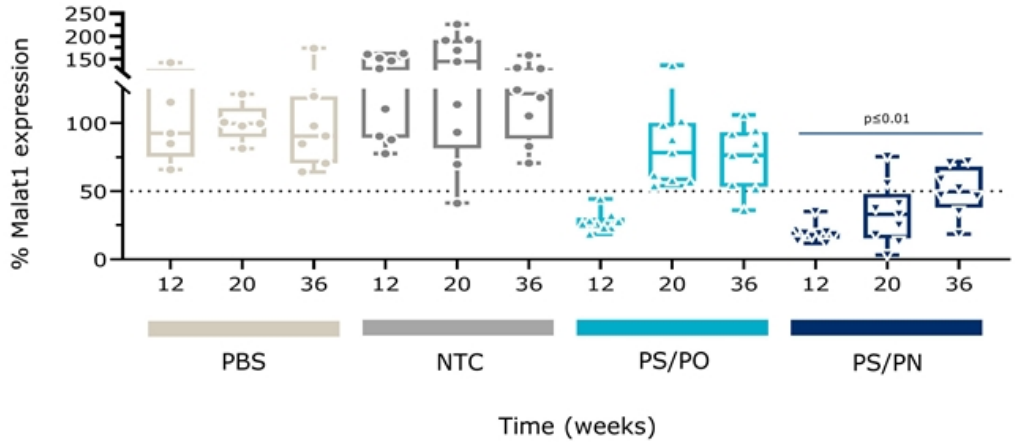


Intravitreal injection

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.

Durable Malat1 knockdown through 9 months with PN backbone chemistry modifications

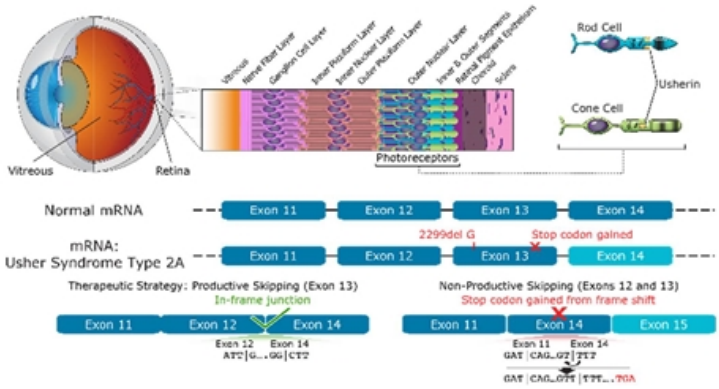
~50% Malat1 knockdown at 36 weeks in the posterior of the eye



Compound or PBS (1 x 50 ug 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. PBS = phosphate buffered saline; NTC= chemistry matched non-targeting control

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**



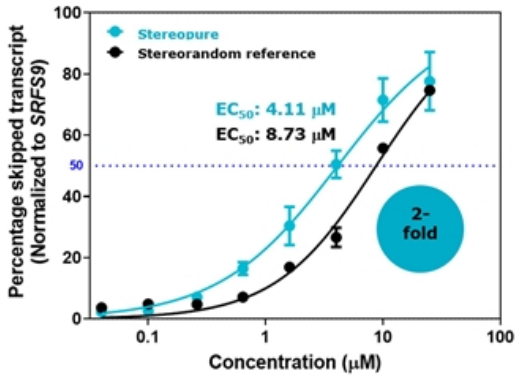
Oligonucleotides that promote USH2A exon 13 skipping may restore production of functional usherin protein

WAVE LIFE SCIENCES

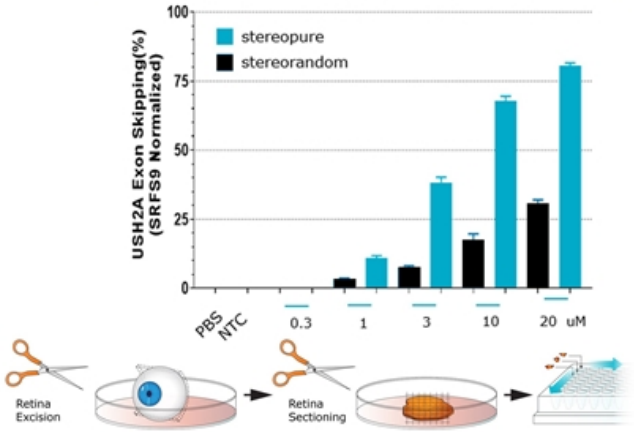
Sources: Boughman et al., 1983. *J Chron Dis*. 36:595-603; Seyedahmadi et al., 2004. *Exp Eye Res.* 79:167-173; Liu et al., 2007. *Proc Natl Acad Sci USA* 104:4413-4418.

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 retinas

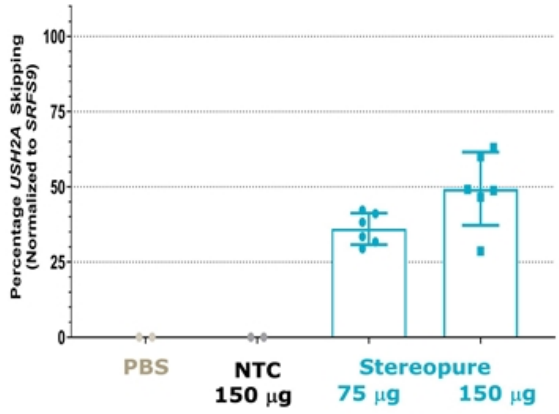


WAVE LIFE SCIENCES

Oligonucleotides 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. Stereorandom: Compound identified in van Diepen et al. 2018. Antisense oligonucleotides for the treatment of eye disease. W02018055134A1. Stereopure: is a stereopure antisense oligonucleotide. Right: Whole NHP were enucleated (n=4) and compounds (1–20 mM) were added to extracted retinas under free-uptake conditions. Exon skipping was evaluated by Taqman assays on RNA. USH2A transcript levels were normalized to SRSF9. Data presented are mean± s.e.m. stereorandom compound is from van Diepen et al. 2018. Antisense oligonucleotides for the treatment of eye disease. W02018055134A1. Compound-1 is a stereopure antisense oligonucleotide.

Stereopure oligonucleotide elicits dose-dependent exon skipping in NHP eye *in vivo*

Dose-dependent and specific exon skipping in NHP eye



- Oligonucleotide is complementary to NHP *USH2A* exon 12*
- Evaluated 1-week post-single IVT injection
- Dose-dependent activity of **stereopure** oligonucleotides
- Substantial exposure in retina
- Exon-skipping integrity confirmed by RNA-seq at both doses

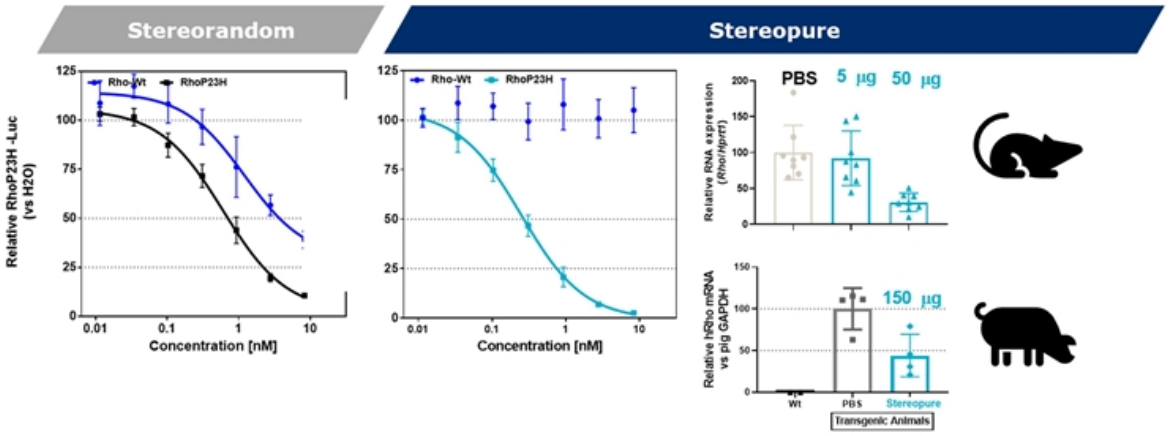
*NHP exon 12 = human exon 13

WAVE LIFE SCIENCES

Stereopure *USH2A* skipping oligonucleotide, PBS or NTC antisense oligonucleotide was delivered to NHP by single IVT injection. One-week post-injection, retina was isolated and exon skipping was evaluated by Taqman assays. *USH2A* skipped transcript levels were normalized to *SRSF9*. Data are mean± s.e.m. Stereopure is an *USH2A* exon-13 skipping stereopure antisense oligonucleotide. PBS, phosphate buffered saline; NTC, non-targeting control; IVT, intravitreal

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

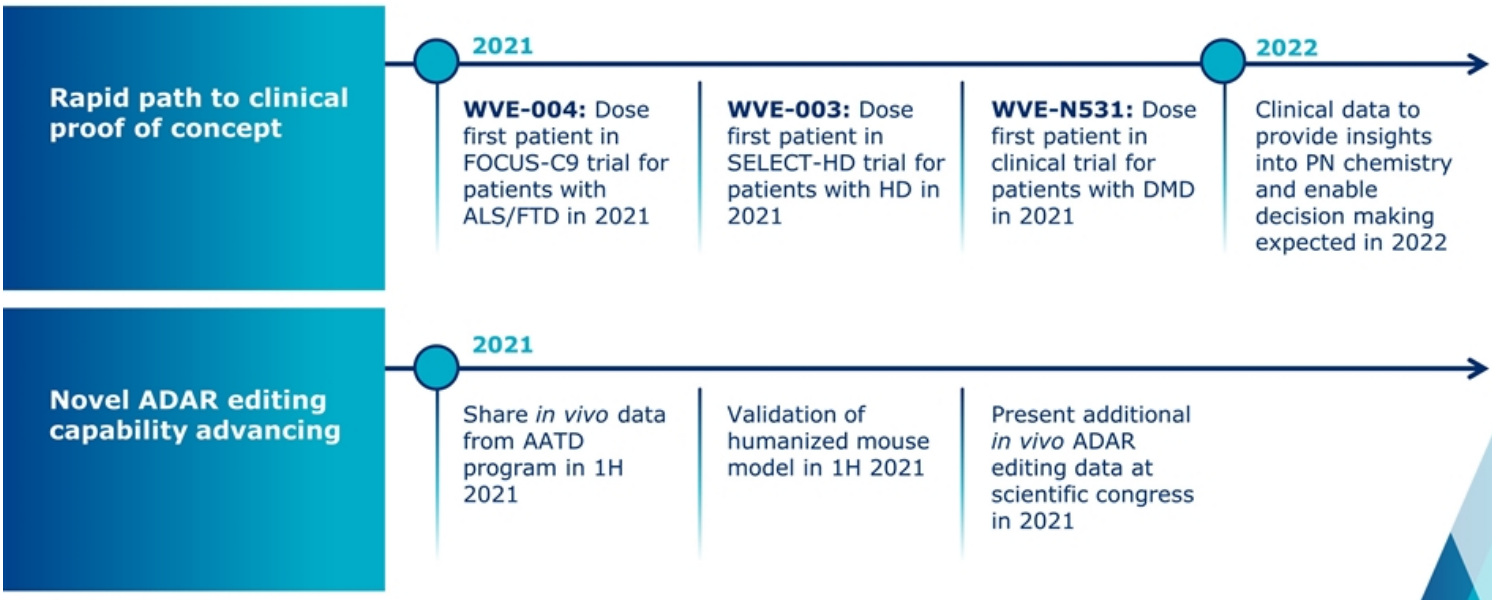
- **Retinitis pigmentosa (RP)**: group of rare, genetic eye disorders resulting in progressive photoreceptor cell death and gradual functional loss; currently no cure
- ~10% of US autosomal dominant RP cases are caused by the P23H mutation in the rhodopsin gene (RHO)
- Mutant P23H rhodopsin protein is thought to misfold and co-aggregate with wild-type rhodopsin, resulting in a gain-of-function or dominant negative effect in rod photoreceptor cells



WAVE LIFE SCIENCES

Left: Reporter assays on a sequence described in WO2016138353A1. Oligonucleotide and luciferase reporter plasmids (wild-type and mutant RHO) are transfected into Cos7 cells. Cells are harvested after 48 hrs, and relative luminescence is measured. Right: Single IVT injection (1 mL) in mouse Rho P23H mouse model or (150 mL) in human P23H pig model. Eyes collected 1-week post injection for mouse or 2-weeks post injection for pig; RNA isolated; Rho, Hprt1, and Gapdh levels determined by qPCR.

Continuous flow of data to enable program decisions through 2022



WAVE LIFE SCIENCES

AATD: Alpha-1 antitrypsin deficiency

WAVE™
LIFE SCIENCES

Realizing a brighter future for people affected by genetic diseases

For more information:
Kate Rausch, Investor Relations
krausch@wavelifesci.com
617.949.4827